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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 27 JANUARY, 1950 No. 1

Original Communications

COLLATERAL CIRCULATION IN THE PRESENCE OF EXPERIMENTAL ARTERIOVENOUS FISTULA

DETERMINATION BY DIRECT MEASUREMENT OF EXTREMITY BLOOD FLOW

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THE incidence of complications following vascular trauma during World War II has emphasized the necessity for further study of this type of injury.[4, 7, 8, 33] Despite the availability of surgical techniques designed to preserve the main arterial supply, such as arteriorrhaphy[10, 25] and the use of vein grafts[1] or inert materials[23] as arterial bridges, in most instances the viability of the part has been directly dependent upon the collateral circulation.[32]

An abundance of arterial collateral circulation is demonstrable in the presence of an arteriovenous fistula. The factors influencing the development of the collateral circulation have never been satisfactorily explained, in spite of many studies. There is a striking difference in the clinical results which follow occlusion of a normal artery[6] and those which follow the excision of an arteriovenous fistula.[17, 18, 21, 30, 31] The determination of the cause for this difference has prompted studies of collateral development in the two conditions.

HISTORICAL

Breschet,[3] in 1833, reported two patients with arteriovenous fistula treated by ligation of the artery proximal to the lesion; both were followed by gangrene. Giraldes,[13] speaking before the Surgical Society of Paris in 1853, advocated proximal and distal ligation of the artery. A commission was appointed to examine the patient of Giraldes and make recommendations for treatment. Although this commission opposed surgical intervention, the suggestion was made that if an operation be performed it should include opening the sac between two ligatures, with preservation of the collateral circulation.

Since that time, operative procedures have been developed which have been universally accepted.[8, 10, 25, 28, 33] Depending upon the conditions which are

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present at operation, one of several procedures may be elected: ligation of the fistula only, transvenous closure (Matas), quadruple ligation and excision, or a technique designed to bridge the arterial defect and maintain continuity of the main artery. It is obvious that despite the diversity of techniques, each is devised to preserve to the maximum extent the available and existing collateral bed.

Reid,[30] in 1925, stated that an arteriovenous fistula was the most powerful stimulus known for the development of collateral circulation.[31] This impression has since been shared by numerous investigators and clinicians, and is based upon both experimental and clinical observations.

Matas[24] advanced the hypothesis that a collateral arterial bed is developed about an arteriovenous fistula over a period of months after the production of the fistula. He emphasized the necessity of waiting six to twelve months before surgery, in order that the collateral circulation might develop to a maximum, and thus insure the postoperative viability of the extremity. This concept has been widely accepted for many years with excellent clinical results.[7, 8, 17-19] Recently, however, it has been questioned by workers in both experimental and clinical fields on the premise that the effective arterial collateral circulation develops quickly, and to a maximum degree, following production of a fistula. These workers have accordingly recommended early operative intervention with the use of sympathetic denervation as an adjunct in aiding and maintaining collateral flow.[5, 12, 14, 26]

FACTORS IN COLLATERAL CIRCULATION

A consideration of collateral circulation must necessarily be concerned with the origin of the vessels involved, the dynamics and magnitude of the blood flow in these collaterals, and the changes which occur following their development.[15]

The blood flow distal to the site of an arteriovenous fistula after excision is the absolute determinant of tissue survival. Therefore, a method whereby the magnitude of this flow could be measured over a period of consecutive time intervals would be of value. Heretofore, comparative and quantitative data concerning the amount of collateral circulation in an individual case have not been available. This is perhaps due to the fact that previous reports have dealt largely with clinical material and that diverse criteria have been used. There has been an abundance of qualitative data which does not permit critical comparison.[32] This has led to the varying estimates of the optimum time for surgical intervention in this particular lesion.

An additional method for the study of collateral circulation became available with the introduction of angiography.[35] The size and number of the vessels can be determined by this method, but not the actual volume blood flow through the vessels. Deterling and associates,[5] working with experimental arteriovenous fistulas in dogs, have recently shown that a considerable portion of the dilated plexuses demonstrable by angiography is predominantly venous. This further points to the need for a method of more accurate estimation of arterial flow alone.

Sir Thomas Lewis was the first to suggest that a portion of the collateral bed developed from small vessels such as arterioles and capillaries which underwent dilatation.[21] It is now generally agreed that the primary origin of the collateral circulation is the pre-existing branches of major vessels which undergo progressive hypertrophy and dilatation, the degree of which is dependent upon several factors.[15]

In the belief that collateral flow is largely dependent upon this dilatation of pre-existing arterial branches, Mulvihill and Harvey[26] demonstrated the use of sympathetic denervation to allow early and maximum dilatation of these vessels. The rise in skin temperatures which follows sympathetic interruption has been the criterion for the success of this method. Skin temperature measurements reflect the skin flow, however, and do not necessarily give an accurate estimate of muscle or combined total flow,[11] which is a major determinant of the limb survival.

Actual blood flow, expressed in cubic centimeters of blood per unit volume of tissue, per unit time, offers the most accurate estimate of collateral circulation after the main artery is occluded. It was thought advisable, therefore, to develop a method whereby this flow through collateral channels could be measured, not only in the presence of acute occlusion of the normal artery, but also in other vascular conditions, such as chronic progressive occlusion and arteriovenous fistula. Such measurements, under basal conditions and at consecutive time intervals, before and after the interruption of the main arterial channel or the elimination of an arteriovenous fistula, would offer a direct approach to the problem of the magnitude and time of development of collateral circulation.

PATHOLOGIC PHYSIOLOGY OF AN ARTERIOVENOUS FISTULA

The profound disturbance in hemodynamics, both local and general, resulting from an arteriovenous fistula, has been described by numerous authors.[8, 9, 16-18, 20-22, 27, 31] The fistula constitutes an arteriovenous shunt which produces an area of decreased peripheral resistance in the neighborhood of the communication. Although the disturbance at first may be local, the sphere of influence becomes more widely distributed, depending upon the size of the fistula, the caliber of the affected artery, and the duration of the lesion.

Blood flows with relatively high pressure from the arterial system into the venous system where its pressure is rapidly dissipated. A portion of the blood in the artery is carried distally through the normal arterial channel, but a variable amount will enter the venous system through the fistula and be swept back toward the heart, serving no useful function. It is thought by Holman[17, 18] that the increase in blood volume in the presence of an arteriovenous fistula is proportional to the magnitude of this secondary circuit.

Arterial branches which leave the artery proximal to the fistula and pass distally into the extremity will find their contents attracted to an area of decreased resistance at the fistula. The differential in pressure between the proximal and distal portions of a collateral artery produces an actual increase in blood flow. A dilatation of the artery results and, in some instances, the

vessel wall becomes hypertrophied as the increased blood flow continues.[34] These vessels (enlarged and tortuous arteries) are evident both by palpation and by arteriography, following occlusion of the fistula. Although the increased blood flow through collateral arterial channels may serve no useful function while the fistula is present, on elimination of the shunt these collateral vessels which were developed by the increased flow will then carry blood to the distal portions of the extremity.

There is an abnormally high venous pressure in the immediate vicinity of the fistula. This causes distal venous engorgement and edema. Proximally, this pressure is quickly dissipated as arterial blood flows into the capacious venous pool, so that little or no increase in right atrial pressure may be demonstrable.[27] Veins in the area adjacent to the fistula and just distal to it may become dilated and tortuous from the constant increase in local venous pressure. This change is largely a local one, and the venous system elsewhere is grossly normal.

Following occlusion of a normal artery, the results are in direct contrast to those following occlusion of an arteriovenous fistula. Blood must flow through pre-existing arterial collateral branches which have undergone no hypertrophy or dilatation. Once the main arterial channel is occluded, blood then flows into the distal portions of the extremity at approximately the pre-occlusion pressure, and under a variable peripheral resistance depending upon the degree of vasoconstriction present.[14, 15] The distal blood flow in the extremity may or may not be adequate for tissue survival, depending upon several factors, as the degree of vasospasm, the number and pattern of arterial collaterals, and the site of interruption of the main vessel.[29]

It is the unique development of collateral circulation in the presence of an arteriovenous fistula, as compared to the paucity of its development in simple arterial occlusion, that has enabled surgeons to excise arteriovenous fistulas and thus interrupt the main arterial channel without resulting gangrene.

REPORT OF THE EXPERIMENTAL INVESTIGATION

Procedure.—Under sodium pentobarbital anesthesia (30 mg. per kilogram body weight) arteriovenous fistulas were produced in the femoral vessels of adult mongrel dogs (10 to 20 kilograms). The vessels were exposed, the adventitia removed, and bulldog clamps applied proximally and distally. A lateral anastomosis, 2.5 to 4 cm. in length, was produced using a fine arterial silk suture.

In a series of over thirty animals, there were no instances of infection, and in only two was there evidence of a thrombosis or decrease in size of the fistula. The animals exhibited the typical signs of the lesion: dilatation and tortuosity of the superficial veins, continuous bruit with systolic accentuation, palpable thrill, and, in some, venous congestion and moderate edema of the extremity.

Blood flows in both the normal and affected extremities of these animals, under pentobarbital anesthesia, were determined by the plethysmographic method described by Eckstein[6] (Fig. 1). The plethysmograph was made of sheet metal in the shape of a flattened cone, the proximal end of which was

adapted to the dog's hindlimb with a plaster of Paris cuff. A traction suture of heavy silk was passed through one of the toes, and the hindlimb drawn snugly into the plethysmograph thus reducing respiratory artefacts to a minimum. The proximal end was sealed by applying melted printer's roller compound to the skin. A large rubber stopper was used to occlude the distal end. A narrow blood pressure cuff was applied proximal to the plethysmograph but distal to the site of the arteriovenous fistula. Inflation of this venous collecting cuff was controlled by an electrically operated solenoid valve which permitted the passage of air pressure from a large reservoir into the cuff.

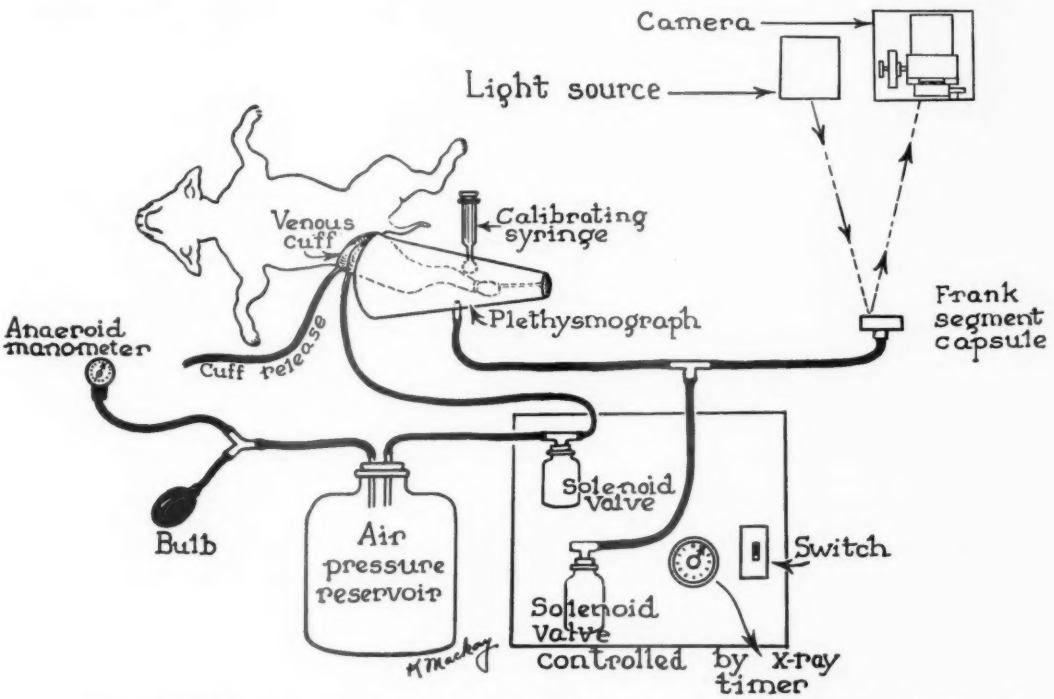


Fig. 1.—Diagrammatic sketch showing plethysmograph, pressure system for inflation of cuff, solenoid valves for cuff inflation and closure of recording system, and the optical recording system.

From a side cock in the plethysmograph, the system was connected to the recording capsule by heavy walled rubber tubing. An electrically operated solenoid valve, in series with an electric timer, controlled continuity of the entire system with the atmosphere, and could be adjusted to remain open for variable periods of time following inflation of the venous cuff. With the system open to the atmosphere during the period of cuff inflation, any pressure artefact from movement of the tissues beneath the cuff was therefore obviated. At the end of this interval, the solenoid valve closed, rendering the system from plethysmograph to recording capsule a closed unit. Changes in volume of the enclosed extremity were then manifested by slight modifications in air pressure and movement of the recording capsule.

For recording, a standard light source, camera, and a Frank segment capsule, approximately 25 mm. in diameter, were used. The entire system was

calibrated by the introduction of 0.5 c.c. of water through a calibrating stopcock into a rubber membrane stretched over its opening inside the plethysmograph. The sensitivity of the system was such that this 0.5 c.c. calibration caused a movement of the light beam on the camera face approximately 3 to 5 cm. (Fig. 2).

In a series of five normal animals, blood flows were determined following acute arterial occlusion. A hindlimb was placed in the plethysmograph as described previously and the femoral artery of this limb was then exposed through a small incision immediately proximal to the venous collecting cuff. A series of normal flow measurements was obtained under conditions present after the operative procedure. A bulldog clamp was then applied to the vessel,

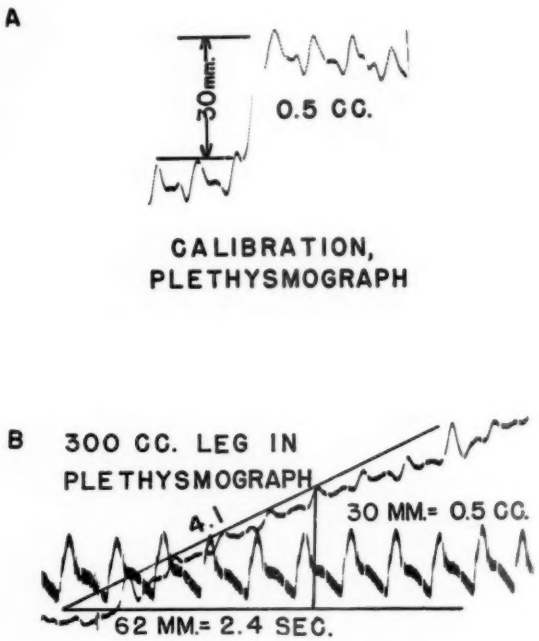


Fig. 2.—*A*, Typical tracing showing method of calibrating plethysmograph and the approximate sensitivity of the system. *B*, Typical blood flow tracing; the method of calculating blood flow is indicated.

producing acute occlusion. Serial measurements were obtained at intervals up to 20 minutes following occlusion (Fig. 3).

Blood flows were measured in the animals with arteriovenous fistulas by a similar method. With the animal anesthetized and the affected hindlimb in the plethysmograph, blood flows were recorded rapidly and at frequent intervals with the fistula open and occluded. An optimum pressure was used in the venous collecting cuff in all instances. Occlusion was accomplished in one of two ways: by aseptically exposing the main vessels and placing four bulldog clamps or traction ligatures about the main artery and vein, or by manual compression of the fistula through the intact skin. The results obtained with either of these methods were essentially the same; the latter method was utilized more frequently because it was convenient and did not require exposure or manipulation of the vessels.

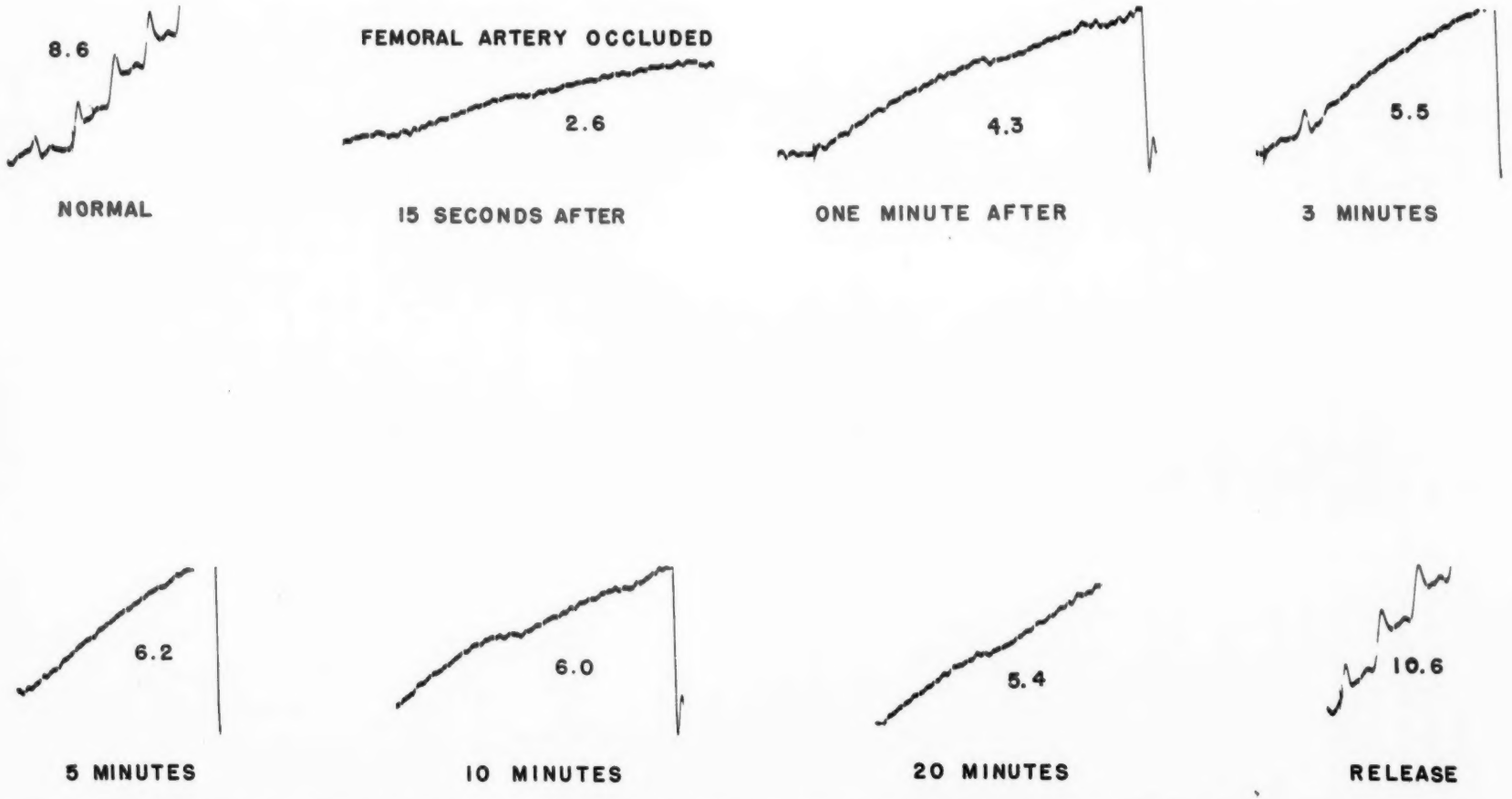


Fig. 3.—Determination of collateral circulation by measurement of distal extremity blood flow after acute occlusion of the normal femoral artery.

A series of 5 to 10 consecutive blood flow measurements, approximately 2 minutes apart, was made with the fistula open. The fistula was then occluded and serial blood flow measurements were made at similar intervals for a period of 10 minutes (Fig. 4). The averages of the values obtained before and after occlusion of the fistula were taken for comparison. Flow curves which failed to show close correlation between consecutive flows or which contained marked respiratory artefacts were discarded.

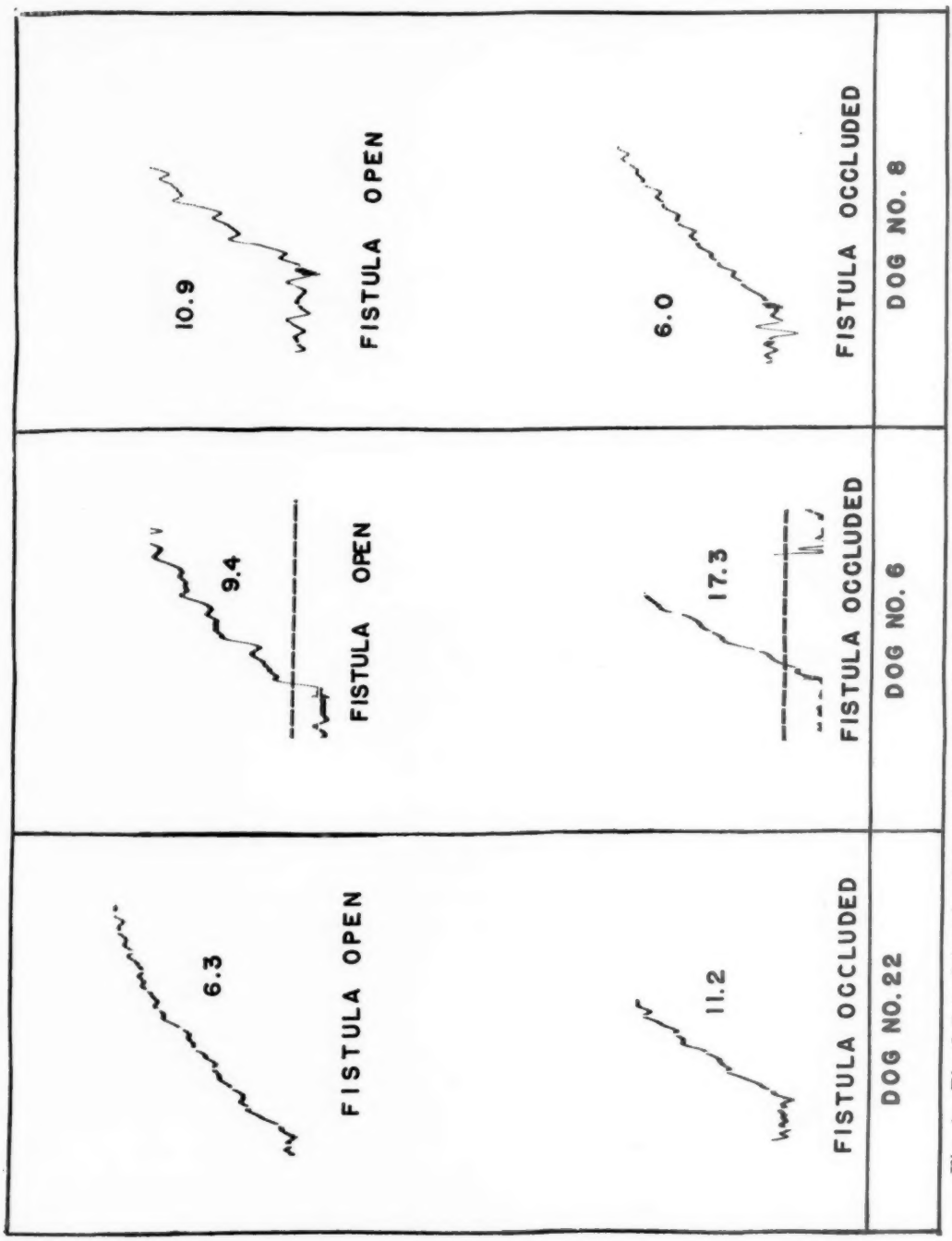


Fig. 4.—Blood flow determinations in three animals with arteriovenous fistulas, with the fistula open and occluded. Dog 8 shows a decrease in blood flow following occlusion of the fistula. The animal was later found at necropsy to have a marked reduction in size of the fistula.

Blood flows in different animals were determined at intervals over a period varying from 2 weeks to 7 months. In some instances, comparative flows in the same animal at various time intervals were obtained.

All determinations were made on anesthetized animals after a period of 30 minutes to 1 hour. The temperature of the room was kept relatively constant between 70 and 75° F. by air-conditioning apparatus. Although extremity flows in a single animal varied from day to day, comparative percentile changes in blood flows after occlusion of the fistula were relatively constant. Moreover, the time intervals involved in the taking of comparative flows, before and after occlusion of a fistula or vessel, were so small (2 to 3 minutes) that any slight change which occurred in basal conditions during this period could be discounted.

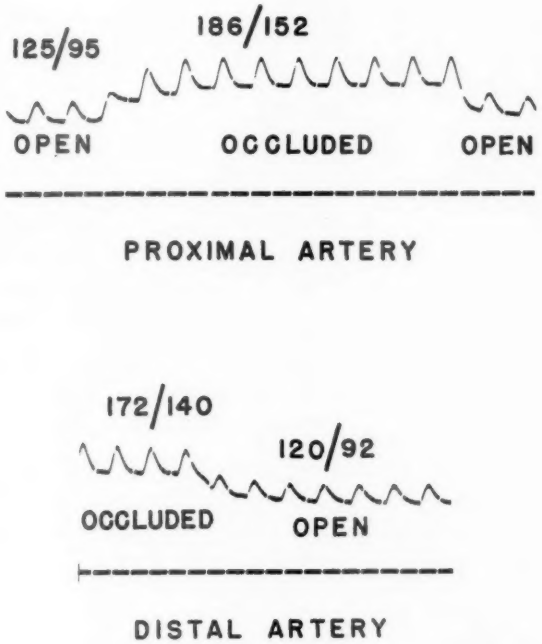


Fig. 5.—Changes in arterial pressure in the proximal and distal artery upon occlusion of the fistula.

In some experiments, arterial pressures were recorded in the proximal and distal arteries using Hamilton manometers and optical recording (Figs. 5 and 6). Blood flows were expressed as cubic centimeters of blood per 100 c.c. of leg volume per minute. Leg volumes were determined by water displacement, the total volume of the plethysmograph being 1,500 c.c.

Results.—In the series of five animals with acute arterial occlusion, the results were consistent. Blood flows taken 30 seconds after occlusion fell to low levels. At the end of 1 minute, the flow had increased but was below normal value. During the next 19 minutes, collateral flow values underwent a gradual but steady increase. At the end of 20 minutes, values were less than the pre-occlusion normal. Upon release of the occluded artery, the blood flows immediately rose to the normal or above normal level. These results are shown graphically in Table I.

The animals with arteriovenous fistulas gave strikingly different results. With the fistula open, blood flow to the distal portion of the extremity was in many instances below normal. Following occlusion of the fistula, with interruption of the main arterial and venous channels to the extremity, no decrease in flow was noted. On the other hand, a marked augmentation of the distal blood flows, varying from 40 to 210 per cent, was exhibited in all but two animals (Table II).

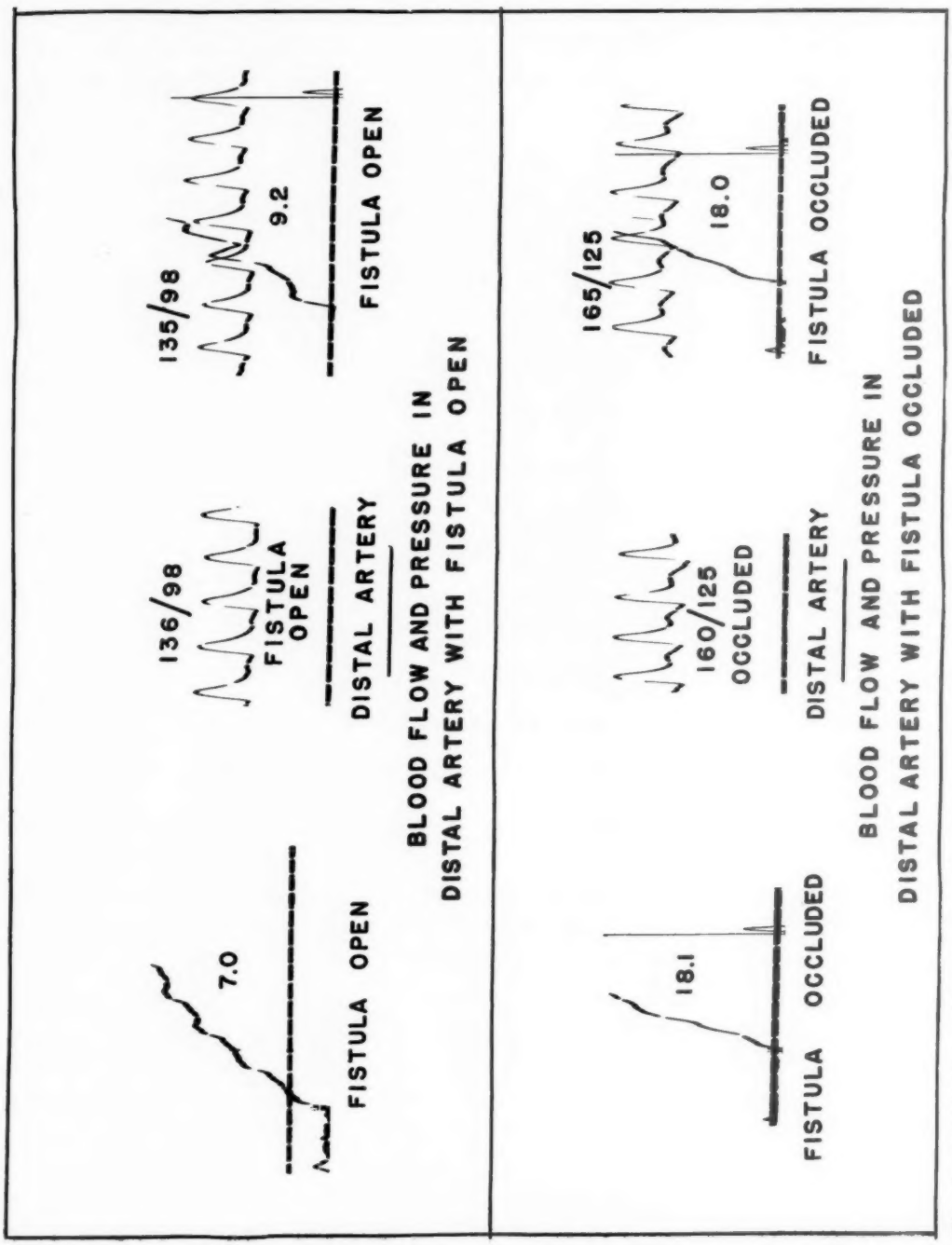
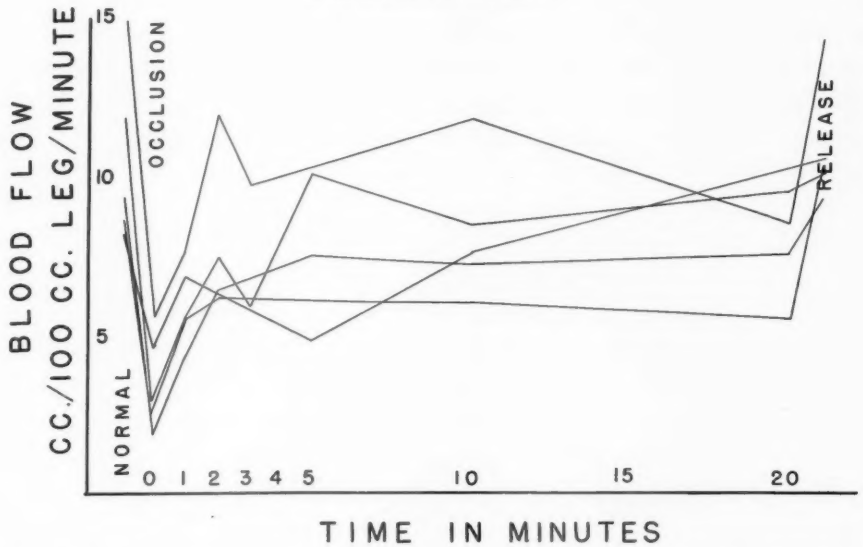


Fig. 6.—Blood flow and pressure in the distal artery with the fistula open and occluded. Tracing on right shows simultaneous recording of pressure and flow.

TABLE I. VARIATIONS IN BLOOD FLOW IN FIVE ANIMALS FOLLOWING ACUTE OCCLUSION OF THE FEMORAL ARTERY



Wide variation in percentile change in blood flows among different animals was evident. At first inspection, no definite relationship was evident between time elapsed and per cent increase in flows. However, the larger increases in flow were seen predominantly in those animals with older lesions.

Comparative flows in several animals after varying intervals of time demonstrated in each instance progressive increase in percentile change after occlusion of the fistula. Decreases in flow were seen in only two animals, and in each there was later demonstrable, following sacrifice, a diminution in the size of the fistula because of fibrosis. Typical flow curves with the fistula open and occluded are shown in Fig. 4. Dogs 22 and 6 showed increased flows following

TABLE II. EXPERIMENTAL RESULTS*

DOG NO.	AGE OF FISTULA	BLOOD FLOW OPEN	BLOOD FLOW OCCLUDED	PER CENT CHANGE
6	2 weeks	9.4	17.3	84
37	3 weeks	4.8	8.6	79
8	1¼ mo.	4.0	8.9	122
24	1½ mo.	5.1	8.0	57
39	1½ mo.	12.9	9.6	-25
47	2¼ mo.	5.3	17.2	210
8	2½ mo.	7.4	3.3	-42
23	2½ mo.	9.5	13.7	44
16	2½ mo.	5.4	8.1	50
1	3 mo.	6.0	8.4	40
22	3¼ mo.	4.2	7.5	78
36	3¼ mo.	14.1	24.3	73
23	4 mo.	5.2	13.6	160
24	5 mo.	7.6	14.0	84
36	5 mo.	4.2	9.9	88
36	7 mo.	8.1	18.0	123

*Tabulation of absolute and percentile changes in blood flow in animals with arteriovenous fistulas of 2 weeks' to 7 months' duration. In several instances, consecutive determinations on the same animals are shown.

occlusion, indicated by the more vertical slope. Dog 8 was one of the two which demonstrated a decrease in blood flow following occlusion of the fistula due to a diminution in size of the fistula by fibrosis.

Simultaneous determination of pressures in the proximal and distal arterial segments uniformly demonstrated a rise in each upon closure of the arteriovenous shunt, roughly proportional to the increase in blood flow in the distal extremity (Figs. 5 and 6).

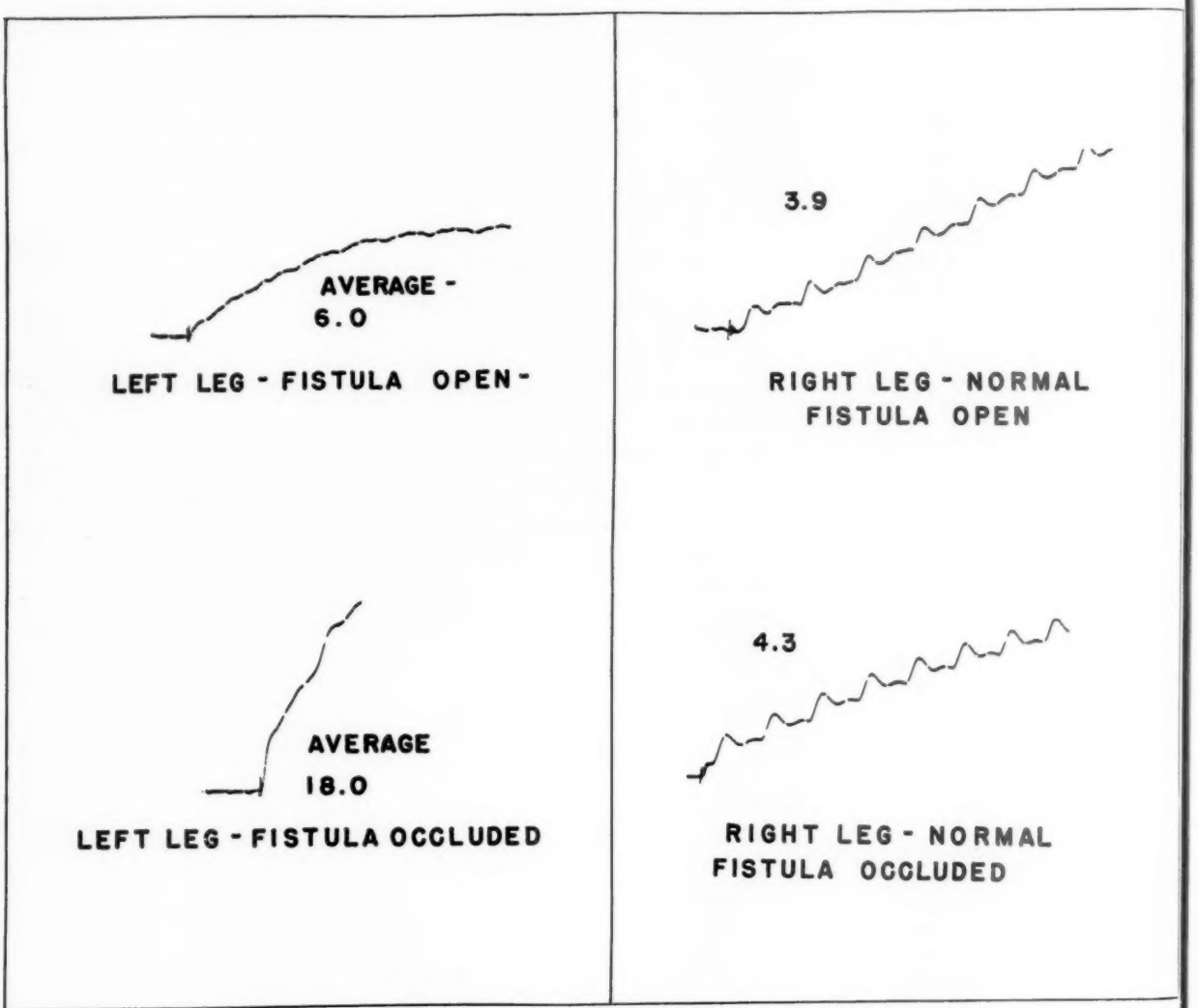


Fig. 7—Simultaneous blood flow changes in normal and affected hindlimbs upon occlusion of fistula in left leg. Absence of significant flow increase in normal limb discredits theory that generalized increase in mean blood pressure is responsible for increased flow in affected limb.

In a few animals, blood flows were measured in the normal and affected hindlimbs simultaneously before and after occlusion of the fistula. As shown in Fig. 7, there was no appreciable increase in flow in the normal limb, despite changes in the mean blood pressure. This may discredit the part played by a generalized increase in blood pressure as a factor in the local increases in blood flow in the affected extremity.

A composite of the results in the chronologic order of time interval (age of the fistula) is given in Table II.

Fig. 8 shows a typical arteriogram in which the arterial tree in both the affected and normal extremity is simultaneously filled with a radiopaque medium (colloidal thorium dioxide) following intra-aortic injection.

DISCUSSION

Following acute arterial occlusion, the magnitude of collateral circulation is dependent upon the flow through pre-existing arterial branches. The decrease in flow which follows acute occlusion may be due partly to spasm of the collateral vessels and partly to the time required for redistributing through smaller branches the blood formerly carried by the main artery. The gradual increase in collateral flow appears to indicate that the available collateral circulation attempts to function to a maximum degree but falls short of normal flow values in almost all instances.

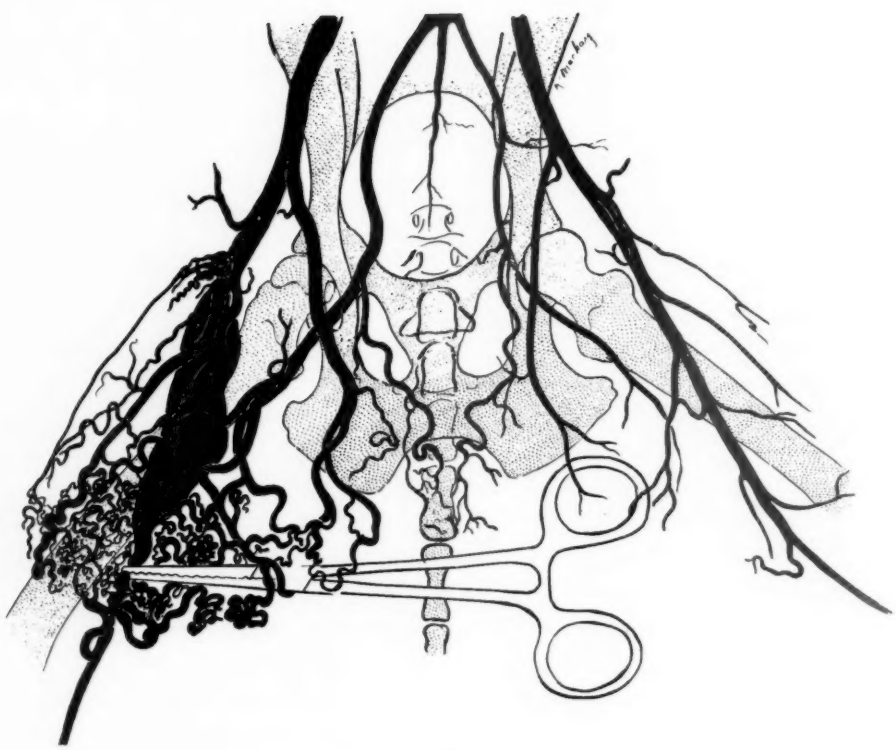
In an extremity with an arteriovenous fistula, the viability of the limb as well as a moderate tolerance for exercise would appear to indicate that the nutrition of the tissues is adequate. This is true even though the flow values with the fistula open may be considerably lower than average normal values. Following occlusion of the fistula, the striking rise in flow which occurs demonstrates that not only is the collateral bed increased and immediately available for use, but also that the distal flow values now are increased even above that level which formerly was sufficient for adequate nutrition of the limb. The collateral bed may have a cross-sectional area far greater than that of the main artery.

Of the several factors concerned in the development of collateral circulation about a fistula, two are of primary importance. First, the influence which the arteriovenous shunt exerts upon the collateral bed by its area of diminished peripheral resistance must have been present for a sufficient period of time to permit maximum dilatation and hypertrophy of these vessels. Second, for peripheral resistance to be diminished sufficiently, it is necessary that the fistula exceed a minimum size. Fistulas which decrease in size may fail to excite the formation of collateral circulation.

In arteriograms, the collateral branches may appear almost as large as the main artery in the contralateral normal limb. When these large, tortuous and dilated vessels are demonstrated either by dissection or angiography, it is readily apparent that the distal extremity flows supplied by these vessels may be several times the normal value in the opposite extremity.

Recent work by Bosher[2] has demonstrated that following excision of an arteriovenous fistula, there is in some instances a regression of the collateral bed over a period of months. This may eventually result in a collateral circulation which is of approximately the same magnitude as that following simple ligation of the artery. His work further indicates that this progression is not appreciably stayed by previous sympathetic denervation. This would seem logical in view of the decreased demand for blood flow through these collateral vessels following excision of the fistula. The crux of the problem, however, is to insure

A.



B.

Fig. 8.—*A*, Roentgenogram of the arterial tree in the normal and affected hindlimb of a dog with femoral arteriovenous fistula. The accompanying vein is ligated and does not fill. The similarity of pattern of arterial branches in each limb and the disparity of size are shown. The smaller channels near the hemostat are undoubtedly in part venous. *B*, Same roentgenogram, diagrammatic sketch.

the presence of a maximum collateral bed immediately after excision. Following this, the regression which takes place slowly over a period of months will allow for a more gradual adjustment of the needs of the circulation and will be less likely to produce a critical arterial insufficiency than would an early excision.

SUMMARY

A method is presented for the direct measurement of collateral blood flow in the presence of both experimental arteriovenous fistula and acute arterial occlusion.

The changes in collateral circulation which follow acute arterial occlusion and the occlusion of an arteriovenous fistula are presented, and the difference in these changes is discussed.

This work offers further evidence in support of the policy of delay in the treatment of arteriovenous fistulas, to allow for the maximum development of collateral circulation.

REFERENCES

1. Blakemore, A. H., and Lord, J. W., Jr.: A Nonsuture Method of Blood Vessel Anastomosis, Ann. Surg. **121**: 435-453, 1945.
2. Bosher, L. H.: Personal communication.
3. Breschet, G.: Memoire sur les aneurysmes, Mém. Acad. roy. de méd., Paris **3**: 101, 1833, cited by Holman.[17]
4. DeBakey, M. E., and Simeone, F. A.: Battle Injuries of the Arteries in World War II. An Analysis of 2,471 Cases, Tr. South. S. A. **57**: 65-110, 1945.
5. Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Arteriovenous Fistula: Experimental Study of Influence of Sympathetic Nervous System on Development of Collateral Circulation, Surg., Gynec. & Obst. **84**: 629-641, 1947.
6. Eckstein, R. W., Gregg, D. E., and Pritchard, W. H.: The Magnitude and Time of Development of the Collateral Circulation in Occluded Femoral, Carotid, and Coronary Arteries, Am. J. Physiol. **132**: 351-361, 1941.
7. Elkin, D. C.: Vascular Injuries of Warfare, Ann. Surg. **120**: 284-310, 1944.
8. Elkin, D. C.: The Treatment of Aneurysms and Arteriovenous Fistulas, Bull. New York Acad. Med. **22**: 81-87, 1946.
9. Elkin, D. C., and Warren, J. V.: Arteriovenous Fistulas, Effects on the Circulation, J. A. M. A. **134**: 1524-1528, 1947.
10. Freeman, N. E.: Arterial Repair in the Treatment of Aneurysms and Arteriovenous Fistulae, Ann. Surg. **124**: 888-919, 1946.
11. Friedlander, M., Silbert, S., Bierman, W., and Laskey, N.: Differences in Temperature of Skin and Muscles of the Lower Extremities Following Various Procedures, Proc. Soc. Exper. Biol. & Med. **38**: 150-153, 1938.
12. Gage, M.: Arterial Aneurysm of the Peripheral Arteries. Methods of Developing the Collateral Circulation, Tr. South. S. A. **52**: 257-268, 1939.
13. Giraldes, M.: Traitment du aneurisme par ligation, Bull. Soc. de chir. de Paris, **4**: 22, 1853-1854, cited by Holman.[17]
14. Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L.: Blood Flow, Peripheral Resistance and Vascular Tonus, With Observations on the Relationship Between Blood Flow and Cutaneous Temperature, Am. J. Physiol. **141**: 518-536, 1944.
15. Green, H. D., Cosby, R. S., and Radzow, K. H.: Dynamics of Collateral Circulations, Am. J. Physiol. **140**: 726-736, 1944.
16. Harrison, T. R., Dock, William, and Holman, Emile: Experimental Studies in Arterio-Venous Fistulae: Cardiac Output, Heart **11**: 337-341, 1924.
17. Holman, Emile: Arteriovenous Aneurysm, New York, 1937, The Macmillan Company.
18. Holman, Emile: Clinical and Experimental Observations on Arteriovenous Fistulae, Ann. Surg. **112**: 840-875, 1940.
19. Kennedy, J. A., and Burwell, C. S.: Measurements of the Circulation in a Patient With Multiple Arterio-Venous Connections, Am. Heart J. **28**: 133-148, 1944.
20. Laplace, L. B.: Observations on the Effect of an Arterio-Venous Fistula on the Human Circulation, Am. J. M. Sc. **189**: 497-507, 1935.

21. Lewis, Thomas, and Drury, A. N.: Observations Relating to Arterio-Venous Aneurism, Heart **10:** 301-389, 1923.
22. Lewis, Thomas: The Adjustment of Blood Flow to the Affected Limb in Arteriovenous Fistula, Clin. Sc. **4:** 277-285, 1940.
23. MacFee, W. F.: Arterial Anastomosis in War Wounds of the Extremities, S. Clin. North America **28:** 381-389, 1948.
24. Matas, R.: Diseases of the Vascular System, in Keen, W. W.: Surgery, vol. 5, Philadelphia, 1920, W. B. Saunders Company, Chap. 70, p. 17.
25. Matas, R.: Some Experiences and Observations in the Treatment of Arteriovenous Aneurisms by the Intrasaccular Method of Suture (Endo-aneurismorrhaphy) With Special Reference to the Transvenous Route, Ann. Surg. **71:** 403-427, 1920.
26. Mulvihill, D. A., and Harvey, S. C.: Studies on Collateral Circulation. I. Thermic Changes After Arterial Ligation and Ganglionectomy, J. Clin. Investigation **10:** 423-429, 1931.
27. Nickerson, J. L., Warren, J. V., Cooper, F. W., Jr., and Robertson, R. L.: Unpublished data.
28. Pemberton, J. deJ., and Black, B. M.: Surgical Treatment of Acquired Aneurysm and Arteriovenous Fistula of Peripheral Vessels, Surg., Gynec. & Obst. **77:** 462-470, 1943.
29. Reichert, F. L.: An Experimental Study of the Anastomotic Circulation in the Dog, Bull. Johns Hopkins Hosp. **35:** 385-390, 1924.
30. Reid, M. R.: Abnormal Arteriovenous Communications, Acquired and Congenital. III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures, Arch. Surg. **11:** 25-42, 1925.
31. Reid, M. R., and McGuire, J.: Arteriovenous Aneurysms, Ann. Surg. **108:** 643-693, 1938.
32. Shumacker, H. B., Jr., and Carter, K. L.: Tests for Collateral Circulation in the Extremities, Arch. Surg. **53:** 359-377, 1946.
33. Shumacker, H. B., Jr., and Carter, K. L.: Arteriovenous Fistulas and Arterial Aneurysms in Military Personnel, SURGERY **20:** 9-25, 1946.
34. Thoma, R.: Textbook of General Pathology and Pathological Anatomy, translation into English by Alex. Bruce, London, 1896, Adam and Charles Black, p. 555.
35. Yater, W. M.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, Am. J. M. Sc. **194:** 372-376, 1937.

THE RELATIONSHIP OF THE METHOD OF SUTURE TO THE GROWTH OF END-TO-END ARTERIAL ANASTOMOSES

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THE advances which have been made in the surgery of congenital cardiovascular disease have raised new problems which must be answered. One of the most important of these questions has been whether or not the size of a vascular anastomosis will increase as the patient grows. This question has arisen in relation to the operation for coarctation of the aorta first done by Crafoord[1] abroad and Gross[2] in this country, as well as for the operations for the tetralogy of Fallot introduced by Blalock[3] and Potts.[4]

When an infant or child is operated upon for coarctation of the aorta, it is of considerable importance whether the site of anastomosis will grow as the rest of the aorta increases in diameter. It is obvious that if the anastomosis should not grow, another coarctation would result as the aorta increased in size. Because of uncertainty on this point almost all surgeons have advocated that the operation not be performed until the child has attained most of his growth, although the technical accomplishment of the operation is probably much easier at an earlier age.

In the Blalock and Potts operations for the tetralogy of Fallot the problem is to make an anastomosis between a systemic artery and a pulmonary artery which will permit an adequate left to right shunt. When the anastomosis is made during infancy or early childhood it may be of such a size as to be adequate at that time, but quite inadequate later on, if the size remains stationary as the child grows. The fact that some children have had to be reoperated upon on the other side after a few years of growth suggests that such may have been the case.

In view of the importance of this point on the future of vascular anastomoses made during infancy or childhood, it seemed to be worth while to determine whether such anastomoses do grow, and whether the method or type of suture influences the growth.

EXPERIMENTAL

Although the experiments which we have performed are small in number the results appear so clear-cut that a preliminary report seems justified.

We first attemped to get an answer to this question by operating upon puppies, but we found that most of the smaller puppies died and the larger puppies did not grow sufficiently to give us a clear-cut answer to the problem. It was for that reason that we turned to pigs with the expectation that they would grow rapidly.

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METHOD

Eight pigs averaging 23 pounds in weight were operated upon on Dec. 21, 1948. They were anesthesized with nembutal and the abdominal aorta was exposed retroperitoneally through a transverse left flank incision.

The abdominal aorta, which measured about 5 mm. in external diameter, was divided between clamps and an end-to-end anastomosis done. Four methods of anastomosis were used:

1. A continuous over-and-over silk suture as described by Carrel (00000 Deknatel). This suture included all layers of the artery and was placed about 1 mm. from the edges of the divided aorta.
2. A continuous everting mattress silk suture which is the one most commonly used in this country (Gross and Blalock) (00000 Deknatel).
3. A continuous Carrel catgut suture (000000 chromic catgut).
4. Interrupted mattress silk sutures (00000 Deknatel).

One pig died of the anesthesia, but the other seven were returned to the farm the day following operation, and grew well. They were slaughtered on June 20, 1949, at which time the average weight was 196 pounds, an increase of more than 800 per cent.

The abdominal aorta was immediately removed, a glass cannula was inserted just below the renal artery, and the aorta was clamped at its bifurcation. The glass cannula was attached to a reservoir of saline solution, a mercury manometer, and a pressure bulb. The segment of artery was made watertight, by ligating all small branches, and filled with saline solution at 120 mm. Hg pressure. Photographs and measurements were taken at this pressure. The vessels were then cut longitudinally and more photographs and measurements made. The inside measurements of the cut vessel are probably more accurate than the outside measurements and they only are tabulated.

RESULTS

The pigs averaged 23 pounds in weight when operated upon and 196 pounds when sacrificed.

The average external diameter of the aortas at operation was found to be 5 mm. When the aortas were removed and inflated to 120 mm. Hg pressure the diameters were found to average 15 mm. Applying the formula πR^2 to estimate cross sectional area it was found to average 19.6 sq. mm. at operation, and 176.7

TABLE I. INSIDE CIRCUMFERENCE OF AORTAS MEASURED IN MILLIMETERS AFTER BEING OPENED

	2 CM. PROXIMAL	1 CM. PROXIMAL	ANASTOMOSIS SITE	1 CM. DISTAL	2 CM. DISTAL
1. Carrel silk suture	28		28		28
1A. Carrel silk suture	28		28		27
2. Continuous everting mattress silk	22	22	18	30	40
2A. Continuous everting mattress silk	20	20	18	21	28
3. Carrel catgut	22		22		22
3A. Carrel catgut	27		27		27
4. Interrupted everting mattress silk	25		25		25

sq. mm. at sacrifice approximately six months later, an increase of 900 per cent. This would seem to correspond fairly well with the weight gain when one realizes that the measurements of the external diameter are not highly accurate.

The individual specimens will be described and the measurements of the opened aortas at, and on either side of, the anastomosis recorded in Table I.

Fig. 1.

Fig. 2.

Fig. 1.—Carrel (over-and-over) silk suture. The aorta is distended with saline solution at 120 mm. Hg pressure. There is no constriction at the point of anastomosis.

Fig. 2.—The aorta shown in Fig. 1 cut open. The silk suture has been straightened out and is broken at one point. It is covered by a very thin layer of intima. It is free in the vessel lumen at one point.

1. *Carrel Suture of Silk—Continuous Over-and-Over.*—When the vessel was inflated it did not appear to be constricted at the site of anastomosis (Fig. 1). The external diameter was approximately 18 mm. The silk suture could be seen in the vessel wall.

When the aorta was opened, the suture appeared to be free in the lumen at one point and covered by a very thin layer of intima in the remainder of its extent (Fig. 2). The suture was broken at only one point and the ends were separated about 1.5 mm.

Fig. 3.

Fig. 4.

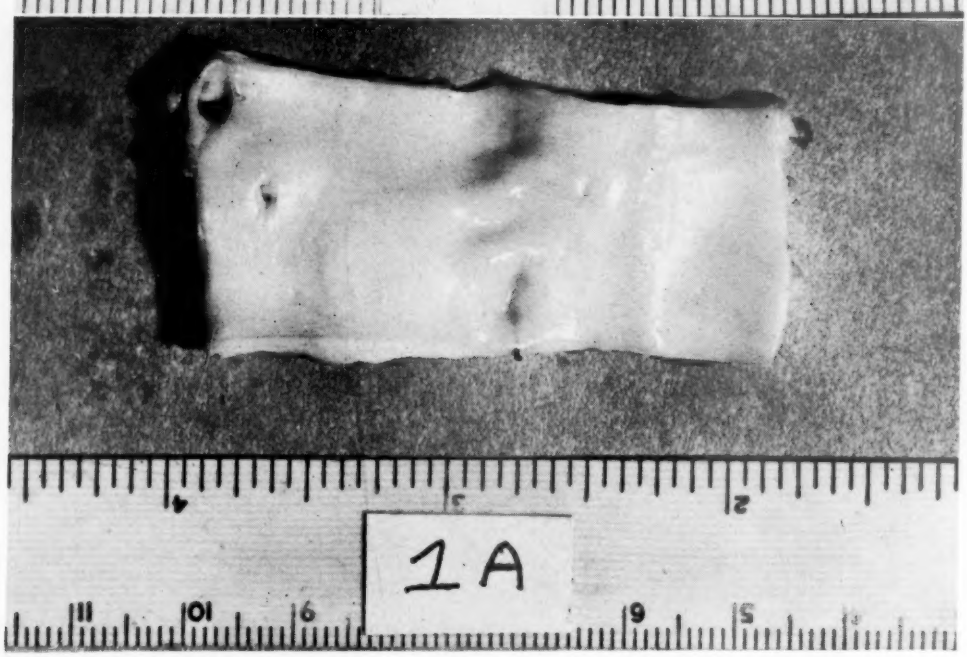

Fig. 3.—Carrel (over-and-over) silk suture. The aorta is distended with saline solution at 120 mm. Hg pressure. There is no constriction at the point of anastomosis.

Fig. 4.—Aorta shown in Fig. 3 cut open. The silk suture has not assumed a subintimal position, and does not show from the intimal side.

1A. *Carrel Suture of Silk, Same as No. 1.*—No apparent constriction was noted when the vessel was inflated (Fig. 3). The approximate external diameter was 15 mm. When the vessel was cut open the silk was not easily visible on the inside (Fig. 4). When examined by transmitted light the silk was seen to be broken and the ends widely separated (Fig. 5).

2. *Continuous Everting Mattress Silk Suture.*—When the vessel was inflated a slight constriction appeared to be present at the site of anastomosis, with an obvious dilation of the aorta distal to it (Fig. 6). The measurements of the external diameter were about 13 mm. at the site of the anastomosis and above, but 22 mm., 3 cm. below the anastomosis.

When the vessel was cut open the constriction was even more apparent (Fig. 7). The silk suture was barely covered by intima and apparently not broken.

2A. *Continuous Everting Mattress Silk Suture* (Same as No. 2).—The specimen appeared quite similar to No. 2. The suture was fragmented but the ends were barely separated. There was narrowing at the site of anastomosis and dilatation distal to it.

3. *Continuous Carrel Suture of Catgut.*—When the vessel was inflated the site of anastomosis could not be identified (Fig. 8). There was no point of constriction and no suture

Fig. 5.—The aorta shown in Figs. 3 and 4. When viewed by transmitted light the silk suture can be seen to have broken and the ends are widely separated.

to mark the site. The diameter of the vessel was 16 mm. When the vessel was cut open one could still not be sure of the site of anastomosis. It was thought to be at a point where the vessel seemed to be a bit thinner, marked by the hemostat (Fig. 9).

3A. *Continuous Carrel Suture of Catgut.*—This was similar to No. 3. The site of the anastomosis could not be determined with certainty and was noted only by some thinning of the vessel at that point.

4. *Interrupted Everting Mattress Sutures of Silk.*—When the vessel was inflated there was no evidence of constriction at the site of the anastomosis (Fig. 10). The silk sutures could be seen in the adventitia. The external diameter of the vessel was 15 mm. When the vessel was cut open the site of anastomosis would have been determined with difficulty except for the silk sutures on the outside wall. The site is marked with the hemostat (Fig. 11).

Microscopic Observations.—Longitudinal sections of the aortas through the anastomosis were studied with hematoxylin and eosin stains and elastic tissue stains. There were areas of scarring and foreign body reaction noted in all the vessels. These changes in the vessel wall were least marked in the aortas sutured

with catgut. The vessels with the continuous everting mattress silk sutures showed elevation of the intima apparently due to the silk suture pulling through the vessel wall.

COMMENT

The results seen in these few experiments appear to be fairly clear-cut. The site of anastomosis of the artery did grow except when hindered by the suture. The catgut sutures were absorbed and appeared to give a perfect result.

Fig. 6.

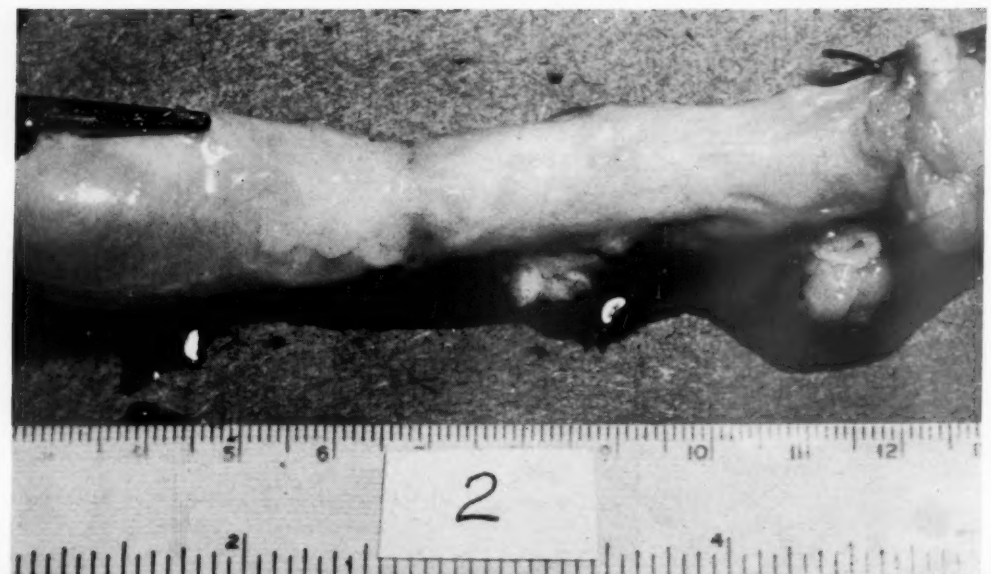

Fig. 7.

Fig. 6.—Continuous everting mattress silk suture. The aorta is distended with saline solution at 120 mm. Hg pressure. There is some constriction apparent at the site of anastomosis with obvious dilatation distal to it.

Fig. 7.—The aorta shown in Fig. 6 cut open. There is obvious constriction at the site of anastomosis with dilatation distal to it. The silk suture is barely covered by intima.

The interrupted silk sutures were found in the outer layer of the vessel wall. They did not constrict the artery lumen, and appeared to give a perfect result at the site of the anastomosis.

A continuous silk suture tends to constrict the lumen of the vessel as it grows. In the Carrel suture we placed the sutures 1 mm. back from the edge so that the total length of silk may have been relatively long. As the vessel grew the silk suture was stretched out straight. Even so in one specimen the length of the suture was not adequate and the suture cut its way into the vessel

Fig. 8.

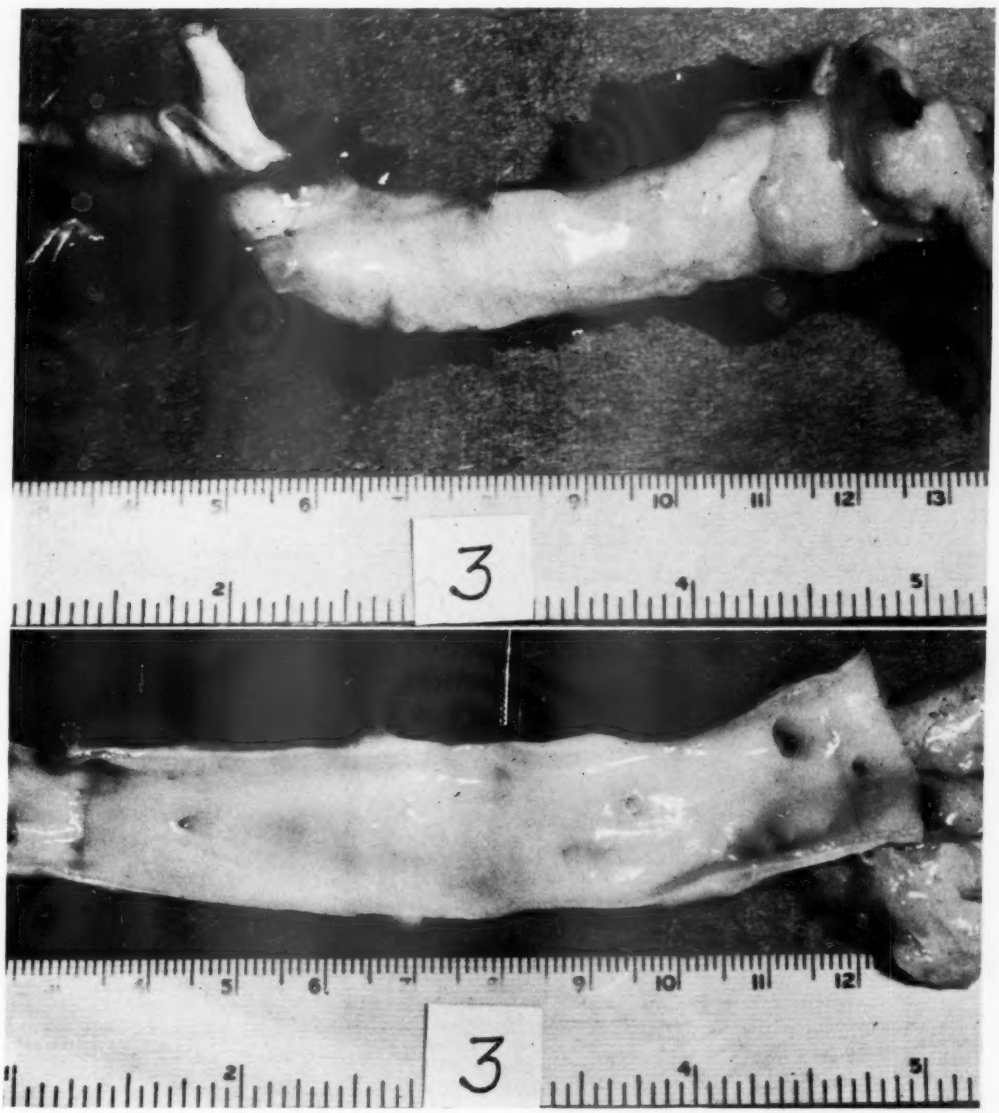

Fig. 9.

Fig. 8.—Continuous Carrel suture of catgut. The aorta is distended with saline solution at 120 mm. Hg pressure. The site of anastomosis is not apparent.

Fig. 9.—The aorta shown in Fig. 8 cut open. The site of the anastomosis is still difficult to ascertain, but was thought to be at the point, indicated by the hemostat, where the vessel seemed to be a bit thinner.

and ended up just under the intima before it broke. In the other specimen, the silk suture broke early and as the vessel grew its ends separated widely in addition to straightening out. Thus, the suture did not constrict the vessel and did not cut into the vessel, so that it was not seen on the intimal side.

The continuous everting mattress silk suture may not be as long as that involved when the Carrel method is used since it varies from the straight line only by the thickness of the vessel wall. In neither of these specimens was the silk obviously broken and the growth of the vessel was limited by the constricting

Fig. 10.

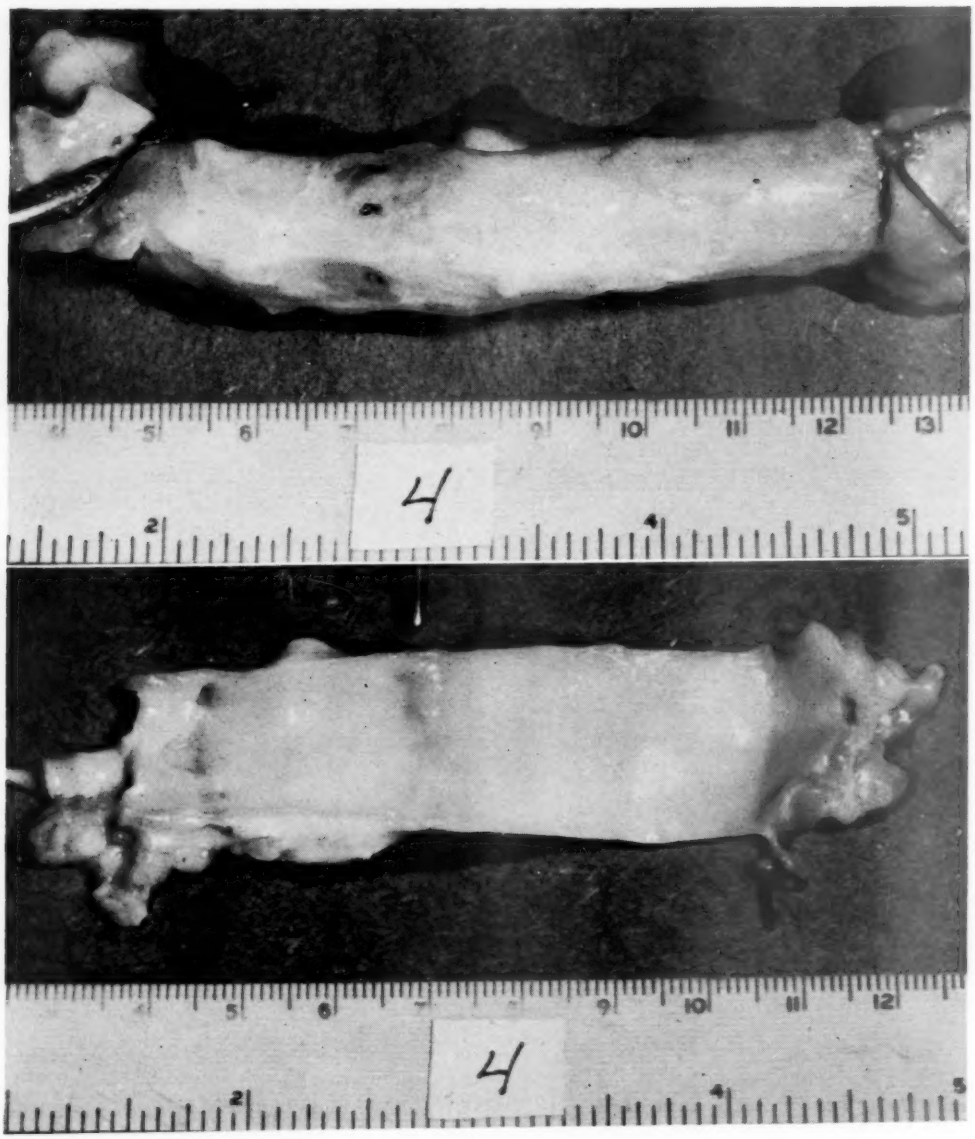

Fig. 11.

Fig. 10.—Interrupted everting mattress sutures of silk. The aorta is distended with saline solution at 120 mm. Hg pressure. There is no constriction at the point of anastomosis. The interrupted silk sutures have assumed a position in the adventitia.

Fig. 11.—The aorta shown in Fig. 10 cut open. The site of anastomosis is readily identified by the silk sutures and marked by the hemostat, but there is no constriction at this point.

suture. The suture became almost a straight line but cut through the vessel wall and was found to be covered only by a thin layer of intima. While the silk may have been fragmented in one or more places in each specimen, the break apparently occurred late, as the ends were hardly separated.

It would seem probable that whether a continuous suture constricts a growing vessel will depend upon (1) its total length and (2) how early it breaks.

It would appear that if a continuous silk suture is used in the growing artery, the silk suture is apt to constrict the artery unless it breaks or unless, by being straightened out, the total circumference of the loop can be increased sufficiently not to constrict the growing artery.

It would seem that, when operating upon a growing patient, if silk sutures are to be used they should be interrupted as often as possible.

SUMMARY

1. Seven pigs were operated upon and an end-to-end anastomosis of the abdominal aorta was done by different suture methods to observe the effect upon the growing aorta. Before being sacrificed, the pigs and their aortas increased in size about 800 per cent.

2. When catgut sutures or interrupted silk sutures were used the result appeared to be perfect. The site of anastomosis was difficult to detect and obviously had grown as the aorta increased in size.

3. When a continuous silk everting mattress suture was used there was constriction at the site of anastomosis with dilatation beyond it. The loop of the silk suture had straightened out as much as possible, but cut through the vessel wall and was covered only by a very thin layer of intima. It obviously constricted the lumen and prevented growth of the vessel at the site of anastomosis.

4. When a continuous silk suture by the Carrel technique was used there was no constriction and the site of anastomosis grew with the vessel. This probably occurred because the final loop of silk was larger than with the everting mattress silk suture. In one the suture had cut through and lay just under the intima. In the other a perfect result was obtained with no silk showing inside the vessel, apparently because the silk had broken early, allowing the ends to separate widely as the aorta grew.

CONCLUSIONS

If further experiments confirm the findings in these few animals, it would appear that in doing end-to-end arterial anastomoses in growing children one should either use catgut sutures or interrupted silk sutures, when this is possible.

REFERENCES

1. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**: 347-361, 1945.
2. Gross, R. E.: Surgical Correction of Coarctation of the Aorta, SURGERY **18**: 673-678, 1945.
3. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart, J. A. M. A. **128**: 189-202, 1945.
4. Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of the Aorta to the Pulmonary Artery in Certain Types of Congenital Heart Disease, J. A. M. A. **132**: 627, 1946.

REFRACTORY ALKALOSIS AND THE POTASSIUM ION IN SURGICAL PATIENTS

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ALTHOUGH it has long been known that potassium plays certain essential roles in neuromuscular physiology, only recently has the clinical significance of alterations of the potassium ion been realized. Hypokalemia, or low level of potassium in the blood, has been produced as a consequence of diets low in potassium in animals,[1, 11, 12] after injections of desoxycorticosterone acetate,[2, 3, 4] prolonged testosterone medication in human beings,[5] and following prolonged therapy with solutions containing only glucose and sodium chloride.[6, 7] It has also become clinically important in association with the following entities:

(1) hereditary or familial periodic paralysis[8, 9]
(2) hypercorticoadrenalism[10, 13]
(3) severe diarrhea, acute[11, 12, 29] and chronic[28]
(4) congenital alkalosis[14, 15]
(5) chronic nephritis[16, 17]
(6) recovery phase of diabetic acidosis[20, 21]

HISTORY

Pediatricians have pioneered the development of knowledge regarding the potassium ion and its clinical importance. McQuarrie[22] has summarized the available information on the subject, especially important from the pediatric viewpoint. Regarding its role in the management of the surgical patient, however, conflicting reports have appeared in the literature. Cutler and Pijoan[23] in 1937 demonstrated that in dogs with experimental intestinal obstruction and pre-renal shock, there was an associated hyperkalemia, and that potassium chloride administered intravenously precipitated death in these animals. Scudder[24] in 1937 also suggested that potassium was a toxic factor which produced symptoms and death in high intestinal obstruction as there was a hyperkalemia in experimental intestinal obstruction. In 1938, Bisgard and his associates[25] produced experimental intestinal obstruction in dogs and came to the conclusion that there was no consistent change in serum potassium or sodium, and that there was no evidence in their experiment that potassium was lethal in duodenal obstruction or intestinal fistulas. In 1939, Falconer and Bargen[26] reported on findings of low potassium levels in patients with intestinal obstruction. They ascribed the deficit to the circumstance of loss of potassium through the agency of vomiting or suction, inasmuch as the concentration of potassium in the gastric juice is two to four times higher

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than the concentration in the serum. The average concentration of potassium in the fasting stomach secretion is 22 meq. per liter (87 mg. per 100 c.c.); in the fasting duodenal secretion is 6 meq. per liter (23 mg. per 100 c.c.); in T tube bile is 3 meq. per liter (12 mg. per 100 c.c.); in the serum is 5 meq. per liter (18 to 22 mg. per 100 c.c.)[26] Childs and Scudder in 1941[27] distended the duodenum of the cat with a balloon and found an elevation of the whole blood potassium and specific gravity. One hour after release of the balloon, the potassium level fell abruptly.

It might be suggested that animal experiments are not wholly tenable because in dogs and cats there is approximately the same concentration of potassium in the red blood cells as plasma, while in human red cells, the concentration of potassium is twenty times that of plasma; consequently, the potassium in animals probably has a different economy from that in human beings.

Because of the relative paucity of clinical information on surgical patients exhibiting hypokalemia, and because the patient in this report presented such interesting problems from the standpoints of fluid and electrolyte therapy, electrocardiographic changes, neuromuscular manifestations, jaundice and operative findings, the following case report is presented.

CASE REPORT

CASE 1 (Univ. Hosp. No. 790512).—C. M., aged 30 years, a white married housewife, was admitted to the Medical Service of the University of Minnesota Hospitals on June 3, 1948, and discharged on Aug. 7, 1948.

The patient stated that six weeks previously, following an uncomplicated delivery of a normal baby, she began to vomit undigested food. This temporarily subsided with the administration of intravenous fluids and supportive measures but recurred in three weeks with evidence of carpopedal spasm which was relieved by intravenous calcium. She was maintained on intravenous fluids for several days in her local hospital prior to admission here, inasmuch as she was unable to retain any food. Past history revealed severe emesis with the first pregnancy two years previously, at about four months gestation. In addition, she had had episodes of slight gaseous distention after meals and occasional vomiting spells since the age of 12. There was no history of pain, hematemesis, or melena. Family history was noncontributory.

Physical examination revealed a thin, white woman exhibiting all the signs of frank tetany. This was alleviated by the intravenous administration of 20 c.c. of 1 per cent calcium gluconate. Otherwise the physical examination was negative.

Laboratory studies on admission showed weight, 47 kilograms; urinalysis: specific gravity, 1.035; pH 6; albumin, trace; sugar 4+ (receiving intravenous glucose at the time); occasional white blood cells and negative tests for acetone, diacetic acid, red blood cells, and casts. Blood: Hemoglobin of 9.5 Gm. per 100 c.c.; white blood cells, 4,900. Differential: polymorphonuclear leucocytes 50, lymphocytes 46, monocytes 2, and plasma cells 2. Blood type A Rh positive. Serum chemistries: bicarbonate 35 meq. per liter (carbon dioxide combining power of 80 vol. per cent), chloride 94 meq. per liter, proteins 6.4 Gm. per 100 c.c., phosphorus 2.9 mg. per 100 c.c., calcium unsatisfactory but the following day was reported as 8.4 mg. per 100 c.c., and a total bilirubin of 0.9 mg. per cent with the one-minute fraction of 0.4 mg. per cent.

X-ray studies (Fig. 1) were read as showing marked gastric dilatation, and an enormously dilated duodenal cap, being five to six times normal size and showing what appears to be a complete obstruction between first and second portions. The gastric analysis was positive for free acid. The electrocardiogram on the seventh hospital day was abnormal with negative T waves and is shown subsequently.

Course.—After admission, efforts were made to feed the patient small amounts by intragastric drip of milk supplemented by parenteral fluids. It was soon found, however, that the obstruction was complete and everything put into the stomach had to be aspirated. The gastric juice always tested negative for bile. Over the course of the next ten days, four blood transfusions were given to bring the hemoglobin to 16.6 Gm. After nearly two weeks of intravenous therapy in our hospital, averaging 3 to 4 liters of 5 per cent glucose in distilled water, and 15 Gm. of sodium chloride daily, the alkalosis was still present, with the serum bicarbonate ranging between 33 and 36 meq. per liter. The serum potassium nine days after admission was 3.4 meq. per liter and the serum sodium was 129 meq. per liter.

The patient was then transferred to the surgical service for relief of unrelenting gastric obstruction and refractory alkalosis, with occasional bouts of tetany necessitating the administration of calcium salts intravenously.

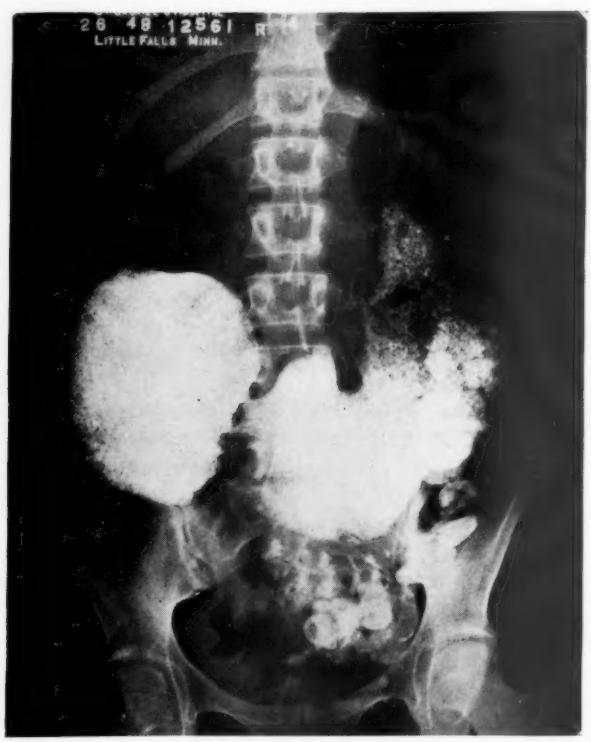


Fig. 1.—Gastrointestinal roentgenogram showing greatly dilated stomach and first portion of the duodenum.

Testosterone, 25 mg. daily for five days, was given in an effort to facilitate nitrogen deposition. She then developed a slight fever, tachycardia, and deep calf tenderness, and it being believed that thrombophlebitis was responsible, the patient was put on a two weeks' course of anticoagulant therapy with dicumarol and heparin.

Two gastric juice analyses with triple histamine stimulation were done after transfer to the surgical service, and in striking contrast to the admission analysis, both of these tests showed no free acid.

The patient's course was progressively downhill with increasing muscular weakness, lethargy, and unresponsiveness, until by July 12, on the fortieth hospital day, it was noted that she could not turn herself in bed because of profound weakness. Painless jaundice, which was becoming more marked, was substantiated on this date with a serum bilirubin determination total of 5.0 mg. per cent and 1 minute of 2.2 mg. per cent. Her pulse became irregular, the electrocardiogram showing presence of a second degree heart block.

At this time she was placed on "critical condition" as she appeared terminal. Additional liver function studies at this time showed a cephalin cholesterol flocculation of 2 plus, thymol turbidity of 2.2 units, bromsulfalein retention of 17 per cent at 45 minutes, and urine Ehrlich of 7.4 Ehrlich units.

A critical review of previous management was then instituted which brought out the fact that the patient had received nothing but parenteral nourishment for approximately fifty days of confinement both at her local hospital and this one, having received no potassium except the small amounts present in blood and Amigen (18 meq. per liter). Blood was then drawn for serum potassium and sodium determinations and the results on July 12 were:

Serum potassium	0.98	meq. per liter (normal, 5 meq. per liter)
Serum sodium	154.	meq. per liter (normal, 143 meq. per liter)

(These determinations were repeated on different specimens and verified.)

Efforts were then directed to restore this potassium deficit by the addition of potassium chloride to daily intravenous fluids. This was done cautiously starting with 3 Gm. the first day and gradually increasing to 5 Gm. a day, but six days later the serum potassium was still only 1.1 meq. per liter, therefore the dosage schedule was increased, with as much as 13 Gm. being administered in one day. In all, over the fourteen days necessary to bring the potassium level to normal, a total of 81.5 Gm. of potassium chloride or 1,100 meq. of potassium had been given. During this period, the serum chloride rose from an average of 90 meq. per liter to 110 meq. per liter and the serum bicarbonate fell to normal after being above normal for well over six weeks. An outline of the intake and output with the blood chemistry values is summarized on the accompanying chart (Fig. 2).

Commensurate with the correction of the potassium deficiency and the alkalosis, these other changes took place.

(1) Chloride content of the gastric juice, which had averaged 1 to 3 Gm. per liter, rose sharply to 5 to 7 Gm. per liter and the gastric analysis once again revealed the presence of free acid.
(2) Chloride content of the urine, which had averaged 6 to 8 Gm. per liter of urine, fell abruptly to a more normal of 1 to 3 Gm. per liter.
(3) Jaundice, quite marked at the time of the low potassium determination, completely disappeared and eleven days after the total bilirubin had been determined at 5.0 mg. per cent, the serum bilirubin was found to be within normal limits, and the cephalin cholesterol flocculation test was negative in contradistinction to the 2+, reported eleven days previously.

Red blood cell potassium determination on July 15 was 91.5 meq. of potassium per liter of red blood cells, while two normal controls were 122 meq. per liter and 131 meq. per liter of red blood cells. The urine excretion of sodium and potassium at the height of the potassium deficit on the fortieth hospital day was:

Urine sodium	78	meq. per liter (214 mg. per cent) x 3.6 liters of urine per 24 hours = 280.8 meq. per 24 hours.
Urine potassium	8.2	meq. per liter (33 mg. per cent) x 3.6 liters of urine per 24 hours = 29.5 meq. per 24 hours.

Further preoperative preparation consisted of five units (500 c.c. each) of blood and 14 units (25 Gm. each) of human salt poor serum albumin during the two weeks before surgery. The average administration of parenteral fluid in addition was 3 to 4 liters of glucose and/or Amigen a day and sodium chloride in amounts as indicated on the accompanying chart. (Fig. 2.)

The series of electrocardiograms taken during this time will be discussed separately.

On July 28, the fifty-sixth hospital day, with a serum bicarbonate of 24 meq. per liter, chlorides 106 meq. per liter, potassium of 5.3 meq. per liter, and a sodium of 142 meq. per liter, the patient was taken to the operating room.

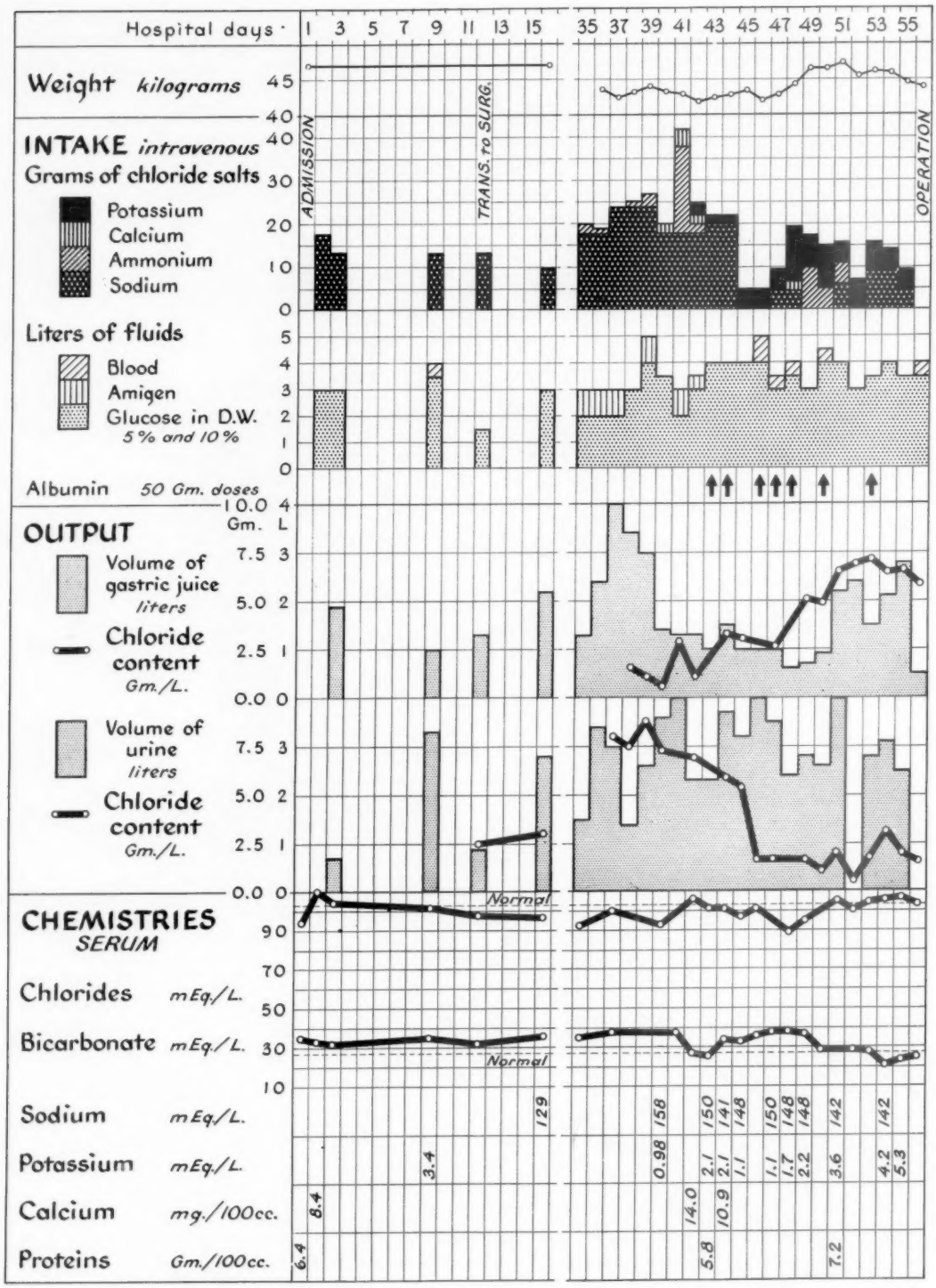


Fig. 2.—Graphic chart of patient's course while in the hospital. Only portions of the first thirty days are shown, as her intake, output, and chemistries remained essentially the same throughout the first half of the hospital stay. Diagrammed above are the graphic representations of her weight, intake, output, and blood chemistries. Note that the high serum bicarbonate, low serum chlorides, high urine chlorides, and low gastric chlorides all returned to normal once the potassium deficit had been corrected.

An exploratory laparotomy was performed by one of us (S. R. F.), who found the stomach and first portion of the duodenum to be greatly dilated. A duodenotomy was performed at the level of the constriction at the second portion of the duodenum just proximal to the papilla duodeni. This exposed a duodenal diaphragm completely occluding the second portion of the duodenum with no apparent lumen. The pancreas was diffusely indurated. The duodenal diaphragm was completely excised, the common bile duct drained with a T tube, and the duodenum sutured with a transverse closure.

The postoperative course was uneventful. The patient began eating on the third postoperative day, and there was no evidence of obstruction. The first bowel movement while in the hospital occurred on the fifth postoperative day, and the incision healed by primary intention. She was discharged on the tenth postoperative day and in two weeks the T tube was removed after a normal cholangiogram had been demonstrated. Two months later, in October, the patient was seen in the out-patient department, having gained fifteen pounds in weight and remaining completely asymptomatic. Blood studies on this visit showed a serum sodium of 146 meq. per liter, serum potassium of 4.5 meq. per liter, and a red blood cell potassium of 101 meq. per liter of red blood cells.

Pathologic Report.—

Gross: The specimen measured 2 cm. in diameter and ½ cm. in thickness. Weight of tissue was 2 Gm.

Microscopic: Mucosa was present on both surfaces. On one side it was thicker than on the other and was made up of glands which had the appearance of those found at the pylorus of the stomach. Large cystic glands were seen lined by cuboidal epithelium, containing mucin. The opposite surface, also covered by mucosa, had glands which were more shallow. The mucosa on this surface was diffusely infiltrated by lymphocytes. Glands were seen similar to Brunner's glands. The tissue between the two mucosal surfaces was edematous. There were interlacing bands of smooth muscle fibers.

Conclusion was duodenal diaphragm.

DISCUSSION

There are many interesting aspects in the study of this patient, among which are the hypokalemia, the alkalosis, the electrocardiographic abnormalities associated with hypokalemia, the jaundice and the complete duodenal diaphragm in a 30-year-old woman.

Hypokalemia.—The value of 0.98 meq. per liter is one of the lowest values reported in a human being, although lower values are on record. Butler and Talbot[5] reported a level of 0.4 meq. per liter in a dwarf.

The pathogenesis is not difficult to explain, as there were several factors. First, no potassium intake for more than fifty days except for small amounts in Amigen and blood, while the urine contained appreciable amounts of potassium. Here when such a profound deficit existed, the kidneys still were excreting approximately 1 Gm. of potassium a day, as determined at the peak of the potassium deficit. The study of Howard and Mason[18] showed that substantial amounts of potassium were excreted via the urine in surgical patients.

Second, the patient received testosterone, which has been shown to cause potassium diminution in the serum.[5] A total of only 125 mg. was given, and the effect of this is difficult to ascertain.

Third, the daily infusion of glucose and saline. Stewart and Rourke[7] proved that prolonged therapy with these intravenous solutions produced potassium deficits. Gamble[30] showed that in a subject with a daily urine

potassium excretion of approximately 60 meq. per twenty-four hours, when 20 Gm. of sodium chloride were given daily, the urine excretion of potassium rose to approximately 90 meq. per twenty-four hours and promptly fell to 40 meq. per twenty-four hours when sodium chloride was once again withheld. When ammonium chloride was ingested, the urinary excretion of potassium rose to 130 meq. per twenty-four hours. He therefore concluded that removal of intracellular electrolyte to preserve normal total ionic concentration was accomplished by the body. In order to keep the total milliosmols around 310 to 315 milliosmols per liter, potassium necessarily leaves when sodium is added. Coller and his co-workers[6] published data to show that urine excretion of potassium was greater in patients infused with isotonic saline solution than in those receiving hypotonic solutions. Gamble and Wallace[19] having measured the amounts of sodium and potassium excreted in the urine with an intake of 1,200 c.c. fluid and 100 Gm. of glucose, found that when 4.5 Gm. of salt were added to this intake, the urinary potassium excretion was greatly increased.

Fourth, vomiting and gastric juice aspiration. Although the potassium concentration of the gastric juice was not measured in this patient, one can assume a certain amount of potassium was lost via this mechanism as the normal gastric juice contains approximately 22 meq. per liter (80 to 90 mg. per 100 c.c.).[26]

The red blood cell potassium determination was made in an attempt to "biopsy" cells for their potassium content, and while the result was lower than that of controls, it was not much lower than that obtained three months later and its significance is therefore difficult to evaluate.

Alkalosis.—Closely allied with the hypokalemia is the problem of refractory alkalosis. In patients with Cushing's syndrome, associated with alkalosis and high serum bicarbonate and low serum chloride, the alkalosis does not respond to sodium chloride or ammonium chloride but does respond to potassium chloride.[10, 13] Darrow[31] cited a case of gastric tetany with alkalosis which did not respond to administration of sodium chloride for seven days despite absence of vomiting and the administration of amounts of salt solution which made adequate sodium chloride available. Further study showed a deficit of potassium.

Recently, Darrow and his associates[32] found that when intracellular potassium is depleted and the intracellular sodium is increased, *biologic equilibrium is achieved only by a high serum bicarbonate,* which in turn increases output of urine chloride. In the light of this evidence, it is quite fallacious to push the administration of chloride in an attempt to overcome the hypochloremia and alkalosis of this type, as the kidney is already doing its best to excrete chloride because of a high serum bicarbonate. Obviously, the rational therapy would be designed to increase the intracellular potassium and decrease the intracellular sodium which would allow the serum bicarbonate to fall to normal and make room for the serum chloride to rise to normal.

This point was well demonstrated in the aforementioned case where the urine contained tremendous amounts of chloride (6 to 8 Gm. per liter) while

the bicarbonate was elevated and the potassium was low, but once the potassium level was normal in the serum and presumably in muscle, the bicarbonate level fell, no longer obligating the kidney to excrete excess chloride, and a more normal excretion of chloride was again found.

In the parenteral injection of potassium salts, the rate of administration must be slow enough not to lead to a temporary rise to toxic levels and the total dose must not be large enough to lead to a toxic extracellular concentration. Good urine output is necessary to prevent accumulation of administered potassium. In the event that a state of oliguria exists, it is probably most wise to refrain from intravenous potassium therapy until a normal urine output is once again restored.

Caution should be exercised in the oral administration of potassium salts, as their absorption can raise the blood level very rapidly and cause toxic hyperkalemia. If it can be administered via the agency of food, of course this is to be preferred.

Duodenal Diaphragm.—The finding of a complete diaphragm in the duodenum was another unusual aspect of this case, especially in view of the patient's age of 30 years. Obviously, some connection had existed between the stomach and the small intestine, as obstruction did not become complete until three or four weeks prior to hospitalization here. We are unable to account for the apparent discrepancy between operative and pathologic findings on the one hand, and the clinical evidence on the other, except to suggest that a previous aperture in the diaphragm had closed over, perhaps as a result of the pancreatitis.

This condition was first described by Boyd[47] in 1845. Since that time, several authors have added cases.[45, 46,48, 49, 50] Krieg in 1937[46] reviewed the literature and reported the twenty-first case. Three in this series survived surgery. This condition apparently develops as a result of the fact that at five weeks, the primitive gut of the embryo closes solidly with a proliferation of epithelial cells which shortly begins to recede by process of vacuolization until the bowel takes on its final histologic structure. Intrinsic malformation is due to faulty recession of these cells. Obstruction is classified as due to a diaphragm, due to stenosis, or complete atresia, and the three are distinct entities. The oldest case on record with duodenal septum was a 70-year-old patient with an 8 mm. aperture in the diaphragm.

Drucker and Cohen[48] in 1946 reported the case of a 23-year-old patient, which was the ninth adult. It is beyond the scope of this report to discuss the problem of duodenal or intestinal obstruction, except to call attention to the interesting electrolyte and fluid imbalances which may result therefrom.

Electrocardiograms.—The heart is an important indicator in dealing with excesses and deficits of ions such as calcium and potassium, and the electrocardiogram was used in guiding the replacement therapy.

The electrocardiographic pattern of hypokalemia has been established by records taken in low potassium states associated with chronic nephritis[17] and

familial periodic paralysis.[33, 35] In this condition the electrocardiograms show partial atrioventricular block usually of first or second degree. The T waves are low and there is depression of the S-T segments.

A level of circulating potassium above normal is likewise associated with characteristic electrocardiographic changes. With progressively increasing levels, the series of changes is as follows:[34, 39, 43, 44] (1) elevation of the T wave, (2) auricular standstill, (3) depression of S-T segments, (4) increasing spread of QRST, (5) biphasic curve.

In general, one may conclude that the potassium ion is necessary for normal cardiac function. In the absence of potassium, heart block will ensue and the heart will stop beating in systole. If the concentration of potassium is too high, the heart will once again fail,[40] but this time in diastole due to a direct depressant action of the ion on the myocardium. The action of potassium on the heart is twofold, affecting both the impulse conduction and the muscle contractility.

Thompson[41, 42] showed direct correlation between height of the T waves and the level of serum potassium. Therefore, if one sees a low T wave on the electrocardiogram, the possibility of hypokalemia should be considered.

The fact that potassium is a myocardial depressant has been used to clinical advantage in the treatment of an hyperirritable myocardium associated with digitalis overmedication.[38] Several investigators[36, 37] have shown that there is a decrease in cardiac muscle potassium in toxic doses of digitalis.

The electrocardiographic findings in this patient were as follows: The initial tracing (Fig. 3) was taken on the seventh hospital day on June 9, 1948, at which time the potassium level was approximately 3.5 meq. per liter. There was depression of the S-T segments in Leads I, II, CF_4, and CF_6. The T waves were low throughout, and in Lead CF_4 the T wave was negative.

When the potassium level was 0.98 meq. per liter and the patient appeared terminal, the electrocardiogram on the forty-second day (Fig. 3) showed a second degree heart block with Wenckebach's periods and occasional supraventricular premature systoles, depression of the S-T segment, and low or negative T waves in all leads (July 14, 1948, forty-second day, 10 A.M.).

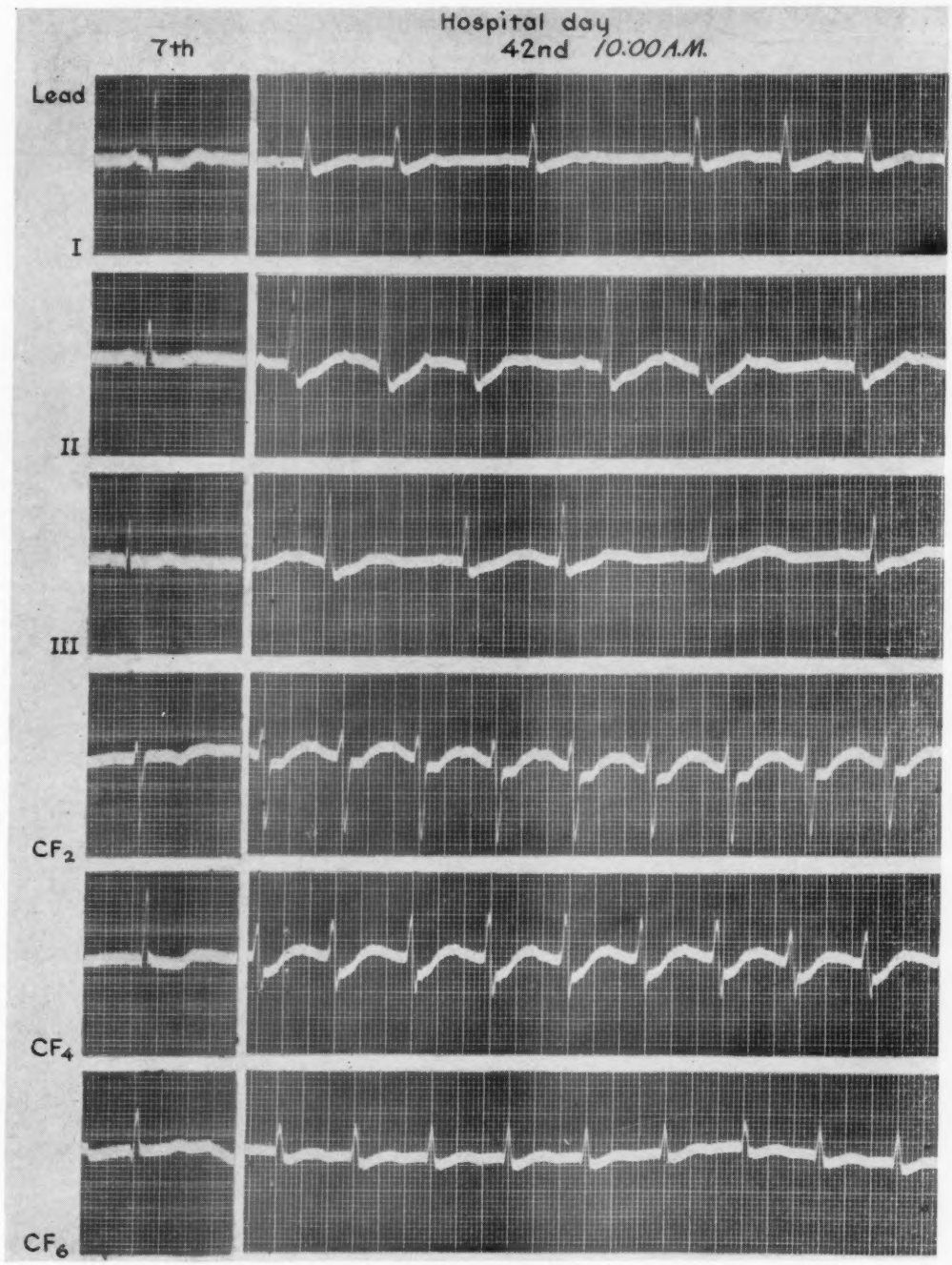
Six hours later, at 4 P.M., after 1 Gm. of potassium chloride had been given intravenously, the heart block and extrasystoles were still present, but there was less S-T depression in Leads CF_2, CF_4, and CF_6 (Fig. 4).

The next day, the forty-third hospital day, after 3 Gm. of potassium chloride had been given, the heart block was reduced to a consistent first degree block and there were no more extrasystoles (Fig. 4).

Two days before surgery, on the fifty-fourth hospital day, with a normal electrolyte pattern restored, the electrocardiogram was likewise normal.

Jaundice.—The cause of the jaundice here is not definite. Liver function tests three weeks after admission were as follows: Serum bilirubin, 1 minute of 0.4 mg. per cent, total of 0.9 mg. per cent; thymol turbidity, 1.7 units; cephalin cholesterol, 1 plus; bromsulfalein, 6.5 per cent retention at 45 minutes; urine Ehrlich, 8.7 Ehrlich units per 2 hours. Two days later, the urine Ehrlich was 27.6 Ehrlich units per 2 hours.

Three weeks after this on the fortieth hospital day, when the jaundice was most apparent and on the same date that the serum potassium was 0.98 meq. per liter, the profile showed: Serum bilirubin, 1 minute of 2.2 mg. per cent,



A. *B.*

Fig. 3.—*A*, Electrocardiogram taken on the seventh hospital day showing S-T segment depression in Leads I, II, CF_4, and CF_6; low T waves with a negative T in Lead CF_4.

B, Electrocardiogram taken on the forty-second day at which time the serum potassium was 0.98 meq. per liter, showing second degree heart block with Wenckebach's periods and occasional supraventricular premature systoles, depression of the S-T segments, and low or negative T waves in all leads.

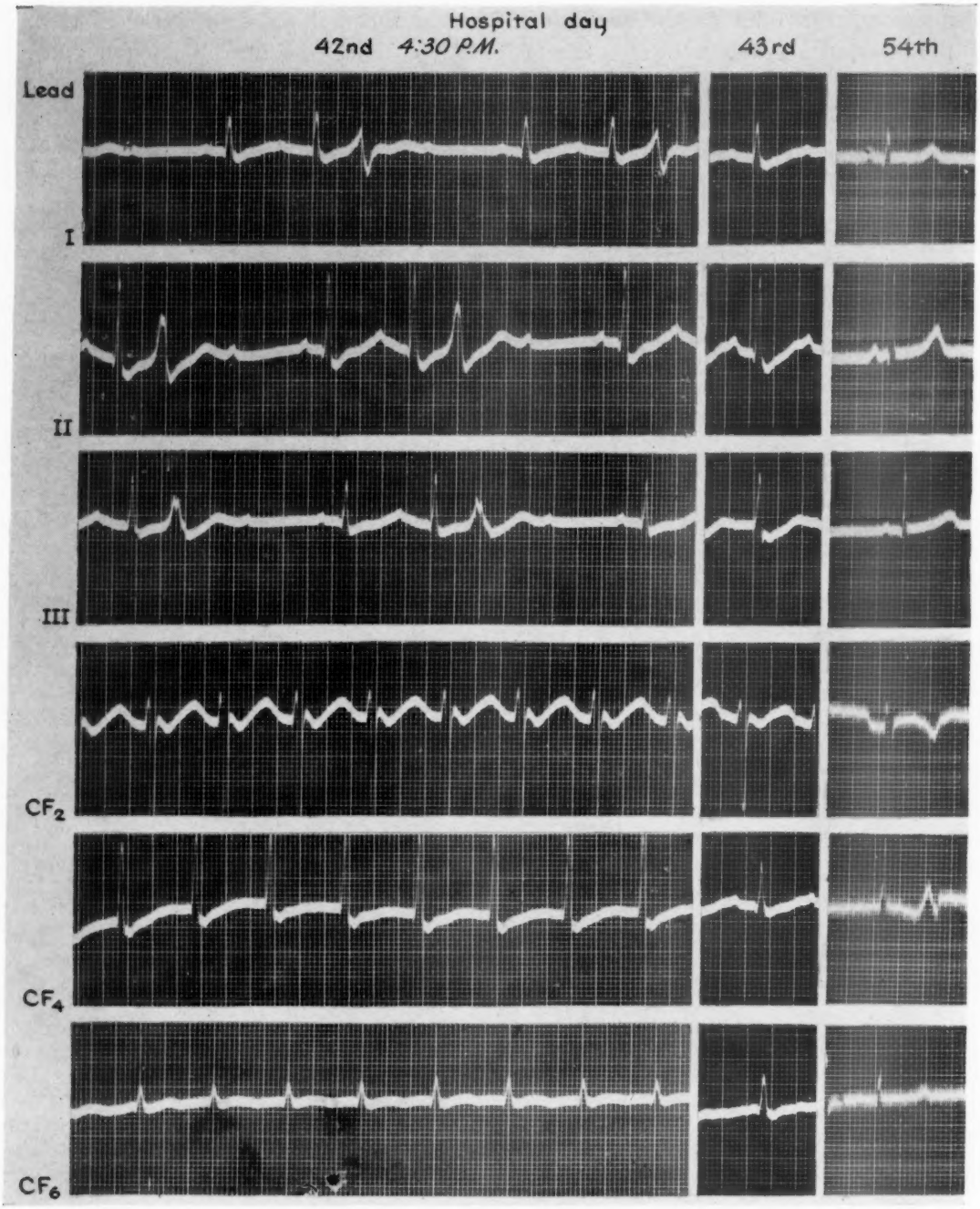


Fig. 4.—*A*, Tracing taken six hours later after the administration of 1 Gm. potassium chloride, showing less S-T depression, but persistence of the arrhythmia. *B*, Electrocardiogram taken on the forty-third hospital day after 3 Gm. of potassium chloride had been administered showed only a first degree heart block and no more extrasystoles. *C*, Tracing made on the fifty-fourth hospital day when the electrolyte pattern had been restored to normal showing a normal electrocardiogram.

total of 5.0 mg. per cent; thymol turbidity, 2.2 units; cephalin cholesterol, 1 plus at 24 hours, 2 plus at 48 hours; bromsulfalein, 17 per cent retention at 45 minutes; urine Ehrlich, 7.4 Ehrlich units per 2 hours.

Potassium therapy was then begun, and in seven days the bilirubin was reported as 1 minute of 1.0 mg. per cent and a total of 2.8 mg. per cent.

At the time of discharge the liver function studies were: Serum bilirubin, 1 minute of 1.2 mg. per cent, total of 2.7 mg. per cent; thymol turbidity, 1.0 unit; alkaline phosphatase, 10.3 King Armstrong units; cephalin cholesterol, 0; urine urobilinogen, 0.1 mg. per 24 hours.

While it was at first thought that the jaundice was likely due to hepatitis from the use of plasma or blood, the liver function studies failed to corroborate this thesis. The clinical course with the rapid diminution in the intensity of the jaundice commensurate with restoration of the fluid and electrolyte pattern to normal, together with the unusual association of results of the liver function tests, lead one to believe that the jaundice was probably due to malnutrition and electrolyte imbalance rather than anything more specific such as infectious hepatitis or homologous serum hepatitis.

Just how frequently the syndrome of refractory alkalosis and hypokalemia occurs in the surgical patient is difficult to ascertain, as little attention has been given this problem. In addition to the case which is reported herein, other patients have exhibited this phenomenon, and although their course was neither quite as complicated nor studied as well, they are reported briefly herewith.

CASE 2 (N. D., Univ. Hosp. No. 777559).—A 64-year-old man had vomiting and diarrhea of two weeks' duration. Preoperative serum sodium was 132.4 meq. per liter, serum potassium was 3.6 meq. per liter, carbon dioxide combining power of 28 meq. per liter, and chlorides of 98 meq. per liter. At surgery, one week after admission, a necrotic segment of jejunum with nonspecific ulcer was resected with end-to-end anastomosis performed by one of us. Postoperative diarrhea with alkalosis and hypochloremia occurred, in spite of apparent adequate replacement of sodium chloride and fluids. Chemistries eight days postoperatively were carbon dioxide combining power of 83 vol. per cent, chlorides of 78 meq. per liter, and serum potassium of 2.16 meq. per liter. Potassium citrate, approximately 6 Gm. daily taken orally, in addition to routine salt and fluid therapy was given for two weeks, then the CO_2 combining power was 29 meq. per liter, the serum chloride was 97 meq. per liter, and the serum potassium was 4.3 meq. per liter. The patient was discharged in good condition.

CASE 3 (J. W., Univ. Hosp. No. 782682).—A 44-year-old woman had fecal fistula of one and one-half years' duration secondary to previous abdominal surgery. Terminal ileum containing fecal fistula was excised and primary anastomosis done.* Postoperative alkalosis, hypochloremia, and tetany persisted for three weeks which did not respond to what was thought to be an overabundant replacement of fluid losses with saline solution, and small doses of potassium citrate (3 to 5 Gm.) orally. Blood chemistries then were serum potassium of 1.9 meq. per liter, carbon dioxide combining power of 36 meq. per liter, and chlorides of 96 meq. per liter. Urine chloride excretion was high with 6 to 8 Gm. per liter. The patient was discharged, never having had electrolyte imbalance restored, but able to eat. Nine months later, the patient was seen in the outpatient clinic and was eating and feeling perfectly well.

CASE 4 (R. K., Univ. Hosp. No. 775041).—A 16-year-old male had chronic ulcerative colitis. Three weeks after a colectomy and ileosigmoidostomy,* he was readmitted because

*By Dr. O. H. Wangensteen.

of diarrhea and intestinal obstruction which relented with conservative management. General condition became worse and parenteral nutrition was necessary all except for small amounts of oral fluids. After three weeks of this management, tetany and alkalosis became evident in spite of oral fluids and intravenous glucose and saline solution to replace the 2½ to 3 liters of liquid stool and 1 to 2 liter urine output per day. Blood chemistries at this time were: Carbon dioxide combining power of 36 meq. per liter, chlorides of 84 meq. per liter, calcium of 8.1 mg. per cent, phosphorus of 5 mg. per cent, serum protein of 5.1 Gm. per cent, serum sodium of 142 meq. per liter, and serum potassium of 2.4 meq. per liter. Potassium citrate, orally, approximately 6 Gm. daily, was given in addition to the previous replacement management. In two weeks the patient was discharged with a carbon dioxide combining power of 26 meq. per liter, and chlorides of 108 meq. per liter after a total of 78 Gm. of potassium citrate had been given orally.

SUMMARY

The case report of a 30-year-old woman with congenital duodenal diaphragm, its surgical extirpation, and complete recovery is presented.

The associated fluid and electrolyte disturbance is discussed with emphasis on the alkalosis and hypochloremia which resisted treatment with usual measures until a deficit of potassium was corrected. One of the lowest serum potassium levels in a human being is recorded here at 0.98 meq. per liter. Electrocardiographic changes, jaundice, and other manifestations of hypokalemia are discussed.

Attention is called to the recognition of an important chemical triad: alkalosis, hypochloremia, and hypokalemia. This state has proved to be refractory to ordinary treatment of alkalosis until potassium replacement is carried out. Three additional case reports are briefly given to substantiate the importance of refractory alkalosis and hypokalemia.

The suggested theory for this mechanism is that when intracellular potassium is depleted, and intracellular sodium is increased, biologic equilibrium exists only when there is a high serum bicarbonate. Because of high serum bicarbonate, the kidney excretes increased amounts of chloride ion, and hypochloremia and alkalosis exist which will not yield until underlying factors are corrected. When the intracellular potassium is increased, and the intracellular sodium is decreased, the serum bicarbonate falls to normal, thereby allowing the serum chloride to rise to normal.

The institution of potassium replacement should not be undertaken unless there is a good urine output, and then the rate of administration should be cautious, because of the danger of toxic levels causing cardiac arrest. It is evident that once potassium deficiency has become this severe, large doses are needed to restore this deficit, as in this particular patient, 81.5 Gm. of potassium chloride were given intravenously over a two-week period before the serum potassium was brought near the normal of 5 meq. per liter. Solutions such as Ringer's or Locke's solutions do not contain enough potassium to be effective when such overwhelming depletion has occurred.

The hypokalemic state in surgical patients may be more common than heretofore realized. By the administration of intravenous saline and glucose solutions, the urinary excretion of potassium is increased in these ill patients. The use of parenteral ammonium chloride therapy in ill patients likewise causes

increased urinary potassium excretion. Loss of body fluids due to vomiting, diarrhea, and fistulas also contributes to the depletion of cellular and extracellular potassium.

In patients with short-term illness who are able to maintain oral nutrition, enough potassium is obtained from their food, but in the dehydrated patient who may have to be maintained on parenteral fluids for many days, a negative potassium balance will ensue, due to urinary excretion of potassium augmented by a loss of potassium in the gastric, pancreatic, intestinal, or biliary juices. It is in this patient that attention to the replacement of potassium ion as well as the replacement of sodium and chloride losses will be rewarded by more rapid convalescence. This deficiency should be suspected when the chemical combination of hypochloremia and high serum bicarbonate are present.

The recognition and importance of potassium deficiency in the surgical patient deserves further investigation, in the laboratory and at the bedside.

REFERENCES

1. Smith, S. G.: Potassium vs. Biotin in the Treatment of Progressive Paralysis in Dogs, Proc. Soc. Exper. Biol. & Med. **63**: 339, 1946.
2. Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters; Certain Effects in Treatment of Addison's Disease, J. A. M. A. **113**: 1725, 1939.
3. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W., and Loeb, R. F.: Certain Effects of Desoxycorticosterone; Development of "Diabetes Insipidus" and Replacement of Muscle Potassium by Sodium in Normal Dogs, Am. J. Physiol. **135**: 230, 1941.
4. Darrow, D. C., and Miller, H. C.: Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate, Rats, J. Clin. Investigation **21**: 601-611, 1942.
5. Butler, A. M., Talbot, N. B., and MacLachlan, E. A.: Effect of Testosterone Therapy on Concentration of Potassium in Serum, Proc. Soc. Exper. Biol. & Med. **51**: 378, 1942.
6. Coller, F. A., Iob, V., Vaughn, H. H., Kalder, N. B., and Mayer, C. A.: Translocation of Fluid Produced by Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, Ann. Surg. **122**: 663, 1945.
7. Stewart, J. D., and Rourke, G. M.: Effects of Large Intravenous Infusions on Body Fluid, J. Clin. Investigation **21**: 197, 1942.
8. Biemond, A., and Daniels, A. P.: Familial Periodic Paralysis and Its Transition Into Spinal Muscular Atrophy, Brain **57**: 91-108, 1934.
9. Aitken, R. S., Allott, E. N., Castleden, L. I. M., and Walker, M.: Observations on Case of Familial Periodic Paralysis, Clin. Sc. **3**: 47-57, 1937.
10. McQuarrie, Irvine, Ziegler, M. R., and Johnson, R. M.: Plasma Electrolyte Disturbance in a Patient With Hypercorticoadrenal Syndrome Contrasted With That Found in Addison's Disease, Endocrinology **21**: 762, 1937.
11. Heppel, L. A.: Electrolytes of Muscle and Liver in Potassium-Depleted Rats, Am. J. Physiol. **127**: 385, 1939.
12. Miller, H. C., and Darrow, D. C.: Relation of Muscle Electrolyte to Alterations in Serum Potassium and to the Toxic Effects of Injected Potassium Chloride, Am. J. Physiol. **130**: 747, 1940.
13. Wilson, D. M., Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in a Case of Cushings Syndrome; a Metabolic Study, J. Clin. Investigation **19**: 701, 1940.
14. Gamble, J. L., Fahey, K. R., Appleton, J. E., and MacLachlan, E. A.: Congenital Alkalosis With Diarrhea, J. Pediat. **26**: 509, 1945.
15. Darrow, D. C.: Congenital Alkalosis With Diarrhea, J. Pediat. **26**: 519-532, 1945.
16. Keith, N. M., Burchell, H. B., and Baggenstoss, A. H.: Electrocardiographic Changes in Uremia Associated With High Concentration of Serum Potassium; Report of Three Cases, Am. Heart J. **27**: 817, 1944.
17. Brown, M. R., Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting From Potassium Loss in Chronic Nephritis, J. A. M. A. **124**: 545-549, 1944.
18. Howard, John E., and Mason, Robert E.: Metabolic Studies Before and After Operation of Chronically Ill Patients Fed Entirely by Vein, Transactions of the Thirteenth Meeting; Conference on Metabolic Aspects of Convalescence, June 10-11, 1946, p. 143.

19. Gamble, J. L., and Wallace, W. M.: Diarrhoeal Dehydration, Fifth International Congress of Pediatrics, New York, 1947.
20. Fenn, W. O.: Deposition of Potassium and Phosphate With Glycogen in Rat Livers, J. Biol. Chem. **128:** 297, 1939.
21. Holler, J. W.: Potassium Deficiency Occurring During Treatment of Diabetic Acidosis, J. A. M. A. **131:** 1186-1189, 1946.
22. McQuarrie, I.: The Clinical Significance of Hypopotassemia, Chicago M. Soc. Bull. **50:** 69-70, 1947.
23. Cutler, E. C., and Pijoan, M.: Certain Chemical Factors in Experimental High Intestinal Obstruction, Surg., Gynec. & Obst. **64:** 892-894, 1937.
24. Scudder, J., Zwemer, R. L., and Truszowski, R.: Potassium in Acute Intestinal Obstruction, SURGERY **1:** 74-91, 1937.
• 25. Bisgard, J. D., McIntyre, A. R., and Osheroff, W.: Studies of Sodium, Potassium, and Chlorides of Blood Serum in Experimental Traumatic Shock, Shock of Induced Hyperpyrexia, High Intestinal Obstruction, and Duodenal Fistula, SURGERY **4:** 528, 1938.
• 26. Falconer, M. A., Bargen, J. A., and Osterberg, A. E.: Intestinal Obstruction in Man; Alterations in Serum Bases and Their Significance, Arch. Surg. **38:** 869, 1939.
27. Childs, S. B., and Scudder, J.: Effect of Distention Upon Whole Blood Specific Gravity and Whole Blood Potassium, Surg., Gynec. & Obst. **73:** 880-884, 1941.
28. Harrison, H. E., Harrison, H. C., Tompsett, R. R., and Barr, D. P.: Potassium Deficiency in Case of Lymphosarcoma With Sprue, Am. J. Med. **2:** 131-143, 1947.
29. Darrow, D. C.: The Retention of Electrolyte During Recovery From Severe Dehydration Due to Diarrhea, J. Pediat. **28:** 515, 1946.
• 30. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., 1942, Harvard University Press.
31. Darrow, D. C.: Changes in Muscle Composition in Alkalosis, J. Clin. Investigation **25:** 329, 1946.
32. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F.: Relation of Serum Bicarbonate Concentration to Muscle Composition, J. Clin. Investigation **27:** 198-208, 1948.
33. Stoll, B., and Nisnewitz, S.: Electrocardiographic Studies in a Case of Periodic Paralysis, Arch. Int. Med. **67:** 755, 1941.
34. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124:** 478-483, 1938.
35. Stewart, J. H., Smith, J. J., and Milhorat, A. T.: Electrocardiogram and Serum Potassium Changes in Familial Periodic Paralysis, Am. J. M. Sc. **199:** 789, 1940.
36. Calhoun, J. A., and Harrison, T. R.: Studies in Congestive Failure IX. The Effect of Digitalis on Potassium Content of Cardiac Muscle of Dogs, J. Clin. Investigation **10:** 139, 1931.
37. Wedd, A. M.: The Influence of Digoxin on Potassium Content of Heart Muscle, J. Pharmacol. & Exper. Therap. **65:** 268, 1939.
38. Sampson, J. J., Alberton, E. X., and Kondo, B.: The Effect on Man of Potassium Administration in Relation to Digitalis Glucosides With Special Reference to Blood Serum Potassium, the Electrocardiogram and Ectopic Beats, Am. Heart J. **26:** 164, 1943.
39. Stewart, H. J., and Smith, J. H.: Changes in the Electrocardiogram and in the Cardiac Rhythm During the Therapeutic Use of Potassium Salts, Am. J. M. Sc. **201:** 177, 1941.
40. Finch, C. A., and Marchand, J. F.: Cardiac Arrest by Action of Potassium, Am. J. M. Sc. **206:** 507, 1943.
41. Thompson, W. A. R.: Potassium and the T Waves of the Electrocardiogram, Lancet **1:** 808, 1939.
42. Thompson, W. A. R.: The Effect of Potassium on the Heart in Man, Brit. Heart J. **1:** 269, 1939.
43. Govan, C. D., and Weiseth, W. M.: Potassium Intoxication, J. Pediat. **28:** 550, 1946.
44. Finch, C. A., Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1:** 337, 1946.
45. Nagel, G. W.: Unusual Conditions in the Duodenum and Their Significance, Arch. Surg. **11:** 529, 1925.
46. Krieg, E. G.: Duodenal Diaphragm, Ann. Surg. **106:** 33, 1937.
47. Boyd, R.: Description of a Malformation of the Duodenum, Lancet **1:** 640, 1845.
48. Drucker, V., and Cohen, E. S.: Megaduodenum Secondary to Intrinsic Duodenal Diaphragm; Report of Case, Am. J. Roentgenol. **55:** 726-729, 1946.
49. Lamson, O. F.: Duodenal Septum, West. J. Surg. **54:** 384-389, 1946.
50. Ladd, W. E.: Congenital Duodenal Obstruction, SURGERY **1:** 878-885, 1937.

FLUORESCEIN: AN ADJUNCT IN SURGERY OF THE GALL BLADDER AND BILIARY PASSAGES

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IN THIS study we have attempted the use of fluorescein as an aid in the surgical management of the gall bladder and biliary tract.

The surgeon in his work upon the gall bladder and extrahepatic biliary passages is often confronted by three major problems: first, the frequent occurrence of anatomic anomalies, especially those of the cystic duct; second, distortion of the bile passages by inflammatory processes and adhesions; and, finally, the most distressing problem of all, the absence or atresia of the biliary passages.

Dissection and immediate cholangiography are the only aids which the surgeon possesses in the operating theater. These are both time consuming and not without danger even in the most skillful hands. Our search for an aid in this work has led us to the use of fluorescein, an innocuous dye which is excreted by the liver and kidneys and which can be detected visually in minimal concentrations by the use of ultraviolet light.

The clinical use of fluorescein diluted by the blood stream has been described by Lange and his associates,[1, 2, 3] in a series of articles published since 1942, to determine the adequacy of peripheral circulation, and since then by many other observers such as Crismon and Fuhrman[4] in studies on gangrene following cold injury and the distribution of fluorescein in body fluids after intravenous injection. Its clinical application in surgery of the gall bladder and bile ducts has been described by us in a preliminary report.[6]

METHODS

Both animal and clinical experimentation was used. The fluorescein preparation used in this work was a 5 per cent solution of fluorescein in 5 per cent sodium bicarbonate in 10 c.c. sterile ampules as prepared for Lange (Fluorescite*). The ultraviolet light used was a mercury lamp, 60 cycle, 110V, with an output of .220 kv-a, and a Wood type filter.†

After the intravenous injection of fluorescein and for some time thereafter, there is a diffuse staining of all tissues due to a high concentration of dye in the circulating blood. After a certain interval of time this is decreased to a minimum and there is still a relatively high concentration of dye in the bile. This is the time we had to choose for our observations. For this purpose, studies of the

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*Manufactured by C. F. Kirk Company, New York, N. Y.

†Conti-Glo-Division of the Continental Lithograph Corporation.

excretion of fluorescein in the blood, urine, and bile were carried out in the dog and human being. After the intravenous injection of fluorescein in a dog, using Nembutal anesthesia, specimens of bile collected by cannula in the common duct, of urine collected by catheter in the bladder, and of blood were taken at intervals as shown in Table I. The dogs received infusions of 5 per cent dextrose in normal saline solution at a constant rate during this experiment. Similar excretion studies in the human being were performed, using patients who were postcholecystectomy or postcholecystostomy with drainages of the gall bladder or the common duct. No infusions were used in these patients. We tried to regulate fluid intake, but were unable to do so due to the human element.

METHOD FOR FLUORESCEIN DETERMINATION IN BILE, URINE, AND BLOOD

The method used for the estimation of the fluorescein level in blood was adapted from the procedure of Crismon and Fuhrman. Their method was (1) alcohol precipitation of the blood proteins and the colorimetric measurement of the fluorescein in the alcoholic supernatant fluid, and (2) photofluorometric measurement of fluorescein in a blood sample diluted with a phosphate buffer.

The colorimetric determination of fluorescein was not adaptable to bile and urine due to the interference of the bile pigments and urochromogens. The sensitivity of the Evelyn colorimeter was not sufficient to permit dilutions so that the chromogens of bile and urine would be negligible and yet measure the concentration of fluorescein present. Calibration curves were made with a known volume of the fluids used in this study and varying concentrations of fluorescein, using a filter with a wave length range between 380 to 460 millimicrons. The differences between the transmissions of the blank sample containing the fluid without fluorescein and of the several concentrations of the fluorescein-containing samples were insignificant. However, it was found possible to measure fluorescein concentration in bile and urine with the photofluorometer. A calibration curve was made wherein a 1:10,000 dilution of bile or urine was used and fluorescein was added so that the concentration ranged from .005 to .025 gamma per milliliter. In order to take into account any fluorescein due to the bile or urine per se, blank samples were made wherein the fluorescein-free sample was diluted as many times as that of the fluorescein-containing samples. The diluent for urine and bile may be either distilled water, saline solution, or phosphate buffer; however, the same diluent should be used for the test samples as was used for the calibration curve. The diluent for blood must be either saline or a buffer solution. (We used a phosphate buffer of pH 7.3.) For the analysis of fluorescein in the test samples, the dilutions for blood varied from 1:1,000 to 1:20,000, and for bile and urine, from 1:3,000 to 1:1,000,000. The instrument used in this study was a Coleman electronic photofluorometer, Model 12B. The filters used were B-1-S and PC-A.

In addition, to determine the optimum time for visualization of the bile passages, dogs were injected intravenously with 10 c.c. of fluorescein and laparotomies were performed at varying intervals of from two to eight hours after injection, at which time the ducts were visualized under ultraviolet light. Patients undergoing routine cholecystectomy were also given fluorescein intra-

TABLE I. RELATIVE CONCENTRATIONS OF FLUORESCEIN IN BLOOD, BILE, AND URINE IN MAN AND DOG
(ALL FIGURES ARE IN MG. PER 100/ML.)

TIME IN HOURS	PATIENT 1			PATIENT 2			PATIENT 3			DOG 1			DOG 2		
	BLOOD	BILE	URINE	BLOOD	BILE	URINE	BLOOD	BILE	URINE	BLOOD	BILE	URINE	BLOOD	BILE	URINE
.5		9.0	95.0		.01	195.6				19.4	238	38	1.50	63.9	203
1.0	4.2	23.8	266.0	2.58	.09	243.0				10.4	267	82	.72	1160.0	669
1.5		21.7	166.0			45.0				10.9	72	150	1.00	1048.0	692
2.0		19.6	59.2	1.66		29.7		13.3	78.8	7.3	72.5	280	.43	688.0	1930
2.5	2.48	17.1	29.6			77.2				4.5	59.4	276	.60	590.0	755
3.0	2.10	10.5	20.0	1.13		138.0				4.2	76.5	128	.28	536.0	654
3.5		6.8	18.5			85.2				2.2	54.0	68	.24	406.0	238
4.0								12.3	31.5	2.2	54.5	38	.21	630.0	180
5.0	1.28	4.1	41.6			77.4				.1	81.9	29	.09	432.0	119
6.0		3.7	27.2	.55		86.8		6.8	20.5	.1	68.7	24.5	.05	476.0	64
8.0		2.4	10.0					3.8	15.7		57.6	.3	Tr.	198.0	23.8
10.0		1.2	13.2		3.20	12.8		2.5	11.2		54.0	Tr.			
12.0					2.70	6.3			14.0						
14.0								1.4	14.5						
16.0					6.00	4.5		.7	11.1						

Patient 1, A 72-yr.-old man, weight about 60 kilograms, eight days postcholecystectomy and common duct drainage for cholelithiasis with jaundice; 10 c.c. of fluorescein.

Patient 2, A 73-yr.-old woman, weight about 60 kilograms, eighteen days postcholecystectomy for empyema of the gall bladder; 10 c.c. of fluorescein; gall bladder bile.

Patient 3, A 61-yr.-old woman, weight about 70 kilograms, eight days postcholecystectomy for cholelithiasis with common duct drainage; 10 c.c. of fluorescein.

Dog 1, Female, 9.4 kilograms, 10 c.c. of fluorescein.

Dog 2, Male, 12.4 kilograms, 10 c.c. of fluorescein.

venously for varying intervals of from one to six hours prior to operation, and observations under ultraviolet light were done during operation

To study the effect of various obstructions of the extrahepatic duct, these were produced in dogs by ligation one week prior to injection and laparotomy. This method was used also to simulate atresia of the bile ducts.

All visualizations were done in a darkened room or operating theater after visual accommodation. The light was placed ten to twelve inches from the point of observation for optimum fluorescence. It has been found that after accommodation of the eyes, dissection is often possible under this light.

RESULTS

Excretion values for fluorescein in man and dog are shown in Table I. These illustrate without question that the blood stream is cleared of most of the dye after four hours, so that there is a minimum of interference in the visualization of the bile passages. Variations in the excretion curves in our patients may be due to variations in liver function, although tests of liver function conducted at the time of the trials were all within the limits of normal. In studying the excretion table it is interesting to note that the concentration of fluorescein in the blood does not, except possibly at the moment of injection, ever reach the high concentrations found in the bile and urine, and that the blood is cleared for practical purposes of most of the fluorescein in four hours.* The high concentration of fluorescein excreted in the urine in both man and dog is noteworthy. Of interest also are the high concentrations of fluorescein in the urine and bile in Dog 2, where the blood stream was quickly cleared of the dye, as compared to Dog 1, where the blood fluorescein level stayed comparatively high for a longer period of time.

Both in dogs and in clinical trials it was found that visualization of the extrahepatic ducts before the end of a period of four hours after injection was useless, because large amounts of fluorescein in the blood stream prevented differentiation of the extrahepatic bile structures. After four hours, the blood stream was cleared of most of the injected fluorescein and concentrations in the bile were sufficiently high to permit visualization and identification of the ducts. The ducts appear with a striking canary yellow color which contrasts well with the surrounding tissues. Although there is still a high enough concentration of fluorescein in the bile after six hours to permit the visualization of the bile passages at this time, this is not as satisfactory a time for observation, because the surrounding tissues, probably their lymph, contain enough fluorescein to stain them and do not, therefore, give the contrasting effect. Fig. 1 is a photograph of the liver and ducts of a dog at laparotomy, four and one-half hours after injection of the dye. Fig. 2 shows the effect of a longer interval of time with less satisfactory results.

In a dog, complete obstruction of the common duct by ligation two weeks prior to fluorescein visualization resulted in a markedly distended gall bladder and a distended common duct above the obstruction, with poor visualization of the ducts and gall bladder and a low concentration of fluorescein in the gall

*In Patient 2 gall bladder bile was drained.

bladder and common bile duct. In another experiment, a cholecystectomy was done, one hepatic duct and the common duct were ligated, and one week later fluorescein visualization was attempted. The common duct was markedly dilated above the ligature and was filled with a watery fluid containing little or no fluorescein, and was poorly visualized. The intrahepatic ducts contained no fluorescein in cases where the common duct was completely obstructed, as in this case.

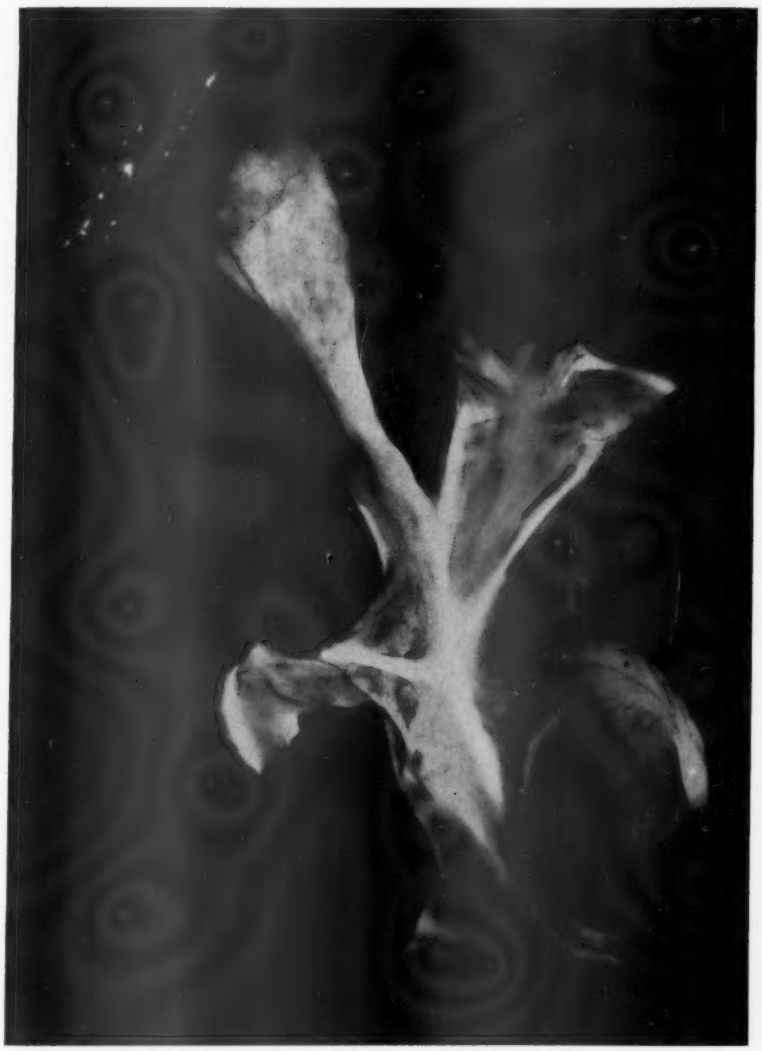

Fig. 1.—Photograph taken under ultraviolet light four and one-half hours after fluorescein injection, demonstrating gall bladder and extrahepatic bile ducts. Cut section of liver shows intrahepatic ducts. These structures appear as a contrasting canary yellow color. The "Yellow" bile is seen in the intrahepatic ducts.

In order to have part of the liver as a normal control and part of the liver obstructed, in another experiment the left hepatic duct only was ligated one week prior to fluorescein visualization. At operation four and one-half hours after the intravenous injection of fluorescein, the ligated duct was found to be

markedly dilated above the obstruction and poorly visualized. The other ducts were normal and well visualized (Fig. 3). Section of the lobe of the liver drained by the ligated duct revealed no fluorescein within these ducts under illumination, whereas section of the lobes drained by the unobstructed ducts revealed the normal intrahepatic ducts filled with bile, containing fluorsecein.

Fig. 2.—Photograph taken five and one-half hours after injection, showing increased fluorescence of duodenum and periductal tissues and fat with less contrasting effect.

It became obvious that complete obstruction of the extrahepatic ducts prevented the excretion of fluorescein and, therefore, visualization of the ducts using this method is not possible. Cases where one would normally find "white bile" will visualize poorly. However, in cases without extrahepatic obstruction, but with intrahepatic obstruction not involving the entire liver, the functioning parts of the liver may be found by this method. We earlier operated in such a case, an infant with intrahepatic obstruction and jaundice, where at operation, identification of the extrahepatic ducts was not possible due to their size and collapsed state. It is believed that fluorescein would have been of value in localizing the functioning ducts in this case.

The high concentrations of fluorescein in the urine led us to try to visualize the ureters in the operating room. In six cases, all gynecological* laparotomies, we attempted the visualization of the ureters at intervals of from four to seven hours after injection of fluorescein. Best results were obtained at seven hours; however, these results were not encouraging. It was felt that there was insufficient contrast between the ureters and the surrounding tissues, primarily because of the thickness of the wall of the ureter and the absence of a column of urine in the ureter.

Fig. 3.—Photograph taken four and one-half hours after injection of dog with previously ligated hepatic duct. The lower arrow indicates the site of obstruction. The upper arrow indicates the dilated duct, which visualized poorly in contrast to patent ducts. Intrahepatic ducts in unobstruced lobes visualized clearly on cut section. There was no visualization of intrahepatic ducts in the obstructed lobe.

*The author is obliged to Dr. Ralph Reis of the Department of Gynecology for his help with these observations.

CONCLUSIONS

1. Fluorescein is excreted by the liver and kidneys after intravenous injection. Large amounts are found in bile four to five hours after injection. The extrahepatic ducts are visualized best at this time in a darkened room using ultraviolet light with a Wood type filter.

2. Complete obstruction of the common duct will prevent visualization of the ducts proximal to the obstruction, that is, both extra- and intrahepatic ducts. The use of fluorescein in operations for atresia of the extrahepatic bile ducts is impractical except that unobstructed ducts, if present, will be found more easily by this method.

3. The use of fluorescein as another liver function test is worthy of consideration.

4. The use of fluorescein in visualization of the ureter was not found to be satisfactory, but may be worthy of further experimentation.

REFERENCES

1. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, M. Clin. North America **26**: 934, 1942.
2. Lange, K., and Boyd, L. J.: The Technique of the Fluorescein Test to Determine the Adequacy of Circulation in Peripheral Vascular Disease, the Circulation Time and Capillary Permeability, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **6**: 78, 1943.
3. Lange, K., and Boyd, L. J.: Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases, Arch. Int. Med. **74**: 175, 1944.
4. Crismon, J. M., and Fuhrman, F. A.: Studies on Gangrene Following Cold Injury: IV. The Use of Fluorescein as an Indicator of Local Blood Flow: Distribution of Fluorescein in body Fluids After Intravenous Injection, J. Clin. Investigation **26**: 259, 1947.
5. Grafflin, A. L.: Studies of Fluorescein Excretion by the Liver Under Normal and Abnormal Conditions; Liver Injury, Josiah Macy, Jr. Foundation Publication, Transactions of the Seventh Conference, January, 1948, p. 73.
6. Menaker, G. J., and Parker, M. L.: Fluorescein: An Adjunct in Surgery of Extrahepatic Biliary Passages, A Preliminary Report, J. A. M. A. **138**: 1039, 1948.

VAGOTOMY

Observations During Four Years

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EVALUATION of vagotomy as a treatment for peptic ulcer has been undertaken by many investigators. It is the purpose of this report to present a brief summary of complications or side effects and a detailed analysis of laboratory tests in our patients. Material has been obtained by repeated examinations of 104 patients treated by vagotomy between June, 1944, and February, 1948. They were followed through June, 1948, and the material was analyzed and submitted for publication in August, 1948.

Clinical experiences, effects on various types of peptic ulcer (duodenal, gastric, and stoma), and a review of the literature have been included in a contemporary report.[1] Conclusions of this report were: (1) Although vagotomy without gastroenterostomy yielded good results in one-half of the patients, occurrence of poor results in the remaining one-half, including retention requiring secondary gastroenterostomy and occurrence of postoperative ulcer, indicates that this procedure has not been a satisfactory surgical treatment for duodenal ulcer. (2) Vagotomy with concurrent gastroenterostomy yielded more consistent and encouraging results as a treatment for duodenal ulcer. (3) Vagotomy effected healing of stomal ulcer. (4) Vagotomy has aided treatment of benign gastric ulcer, and (5) side effects of vagotomy seem to diminish or disappear as time following operation lengthens. These conclusions were based upon clinical evidence which is largely subjective and which may change as longer follow-up studies are available.

It is now evident that occurrence of complications or side effects limits usefulness of vagotomy more than occasional failure of healing of ulcer. It is also evident that duration of the period of reduction of acidity of gastric secretions and of alteration of motility of the stomach must be learned so that the period of protection from recurrence of ulcer may be predicted. Only three study groups[2, 3, 4] reported upon patients followed four to six years.

The material to be reported in this paper is offered for a dual purpose. The first is to present complications or side effects of vagotomy grouped according to type or sequence of operations. This makes available evidence that may aid recognition and treatment of complications and selection of operative techniques. The second is to present results of laboratory tests and special observations describing duration of effects.

Complications or Side Effects Following Vagotomy for Peptic Ulcer

In previous reports results of vagotomy have been described separately according to location or type of ulcer. In this report complications or side effects will be grouped according to type or sequence of operation; that is,

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vagotomy alone, vagotomy with concurrent gastroenterostomy, vagotomy after previous gastroenterostomy, vagotomy followed by secondary gastroenterostomy, or vagotomy and subtotal gastric resection. Since no difference between results of transthoracic and subdiaphragmatic vagotomy was evident, the term vagotomy is employed for either procedure. Side effects occurring in 6 patients with gastric ulcer are omitted. Those in 1 patient treated for gastric ulcer by transthoracic vagotomy and three months later by subtotal gastric resection are included under vagotomy and resection. Of the original 104 patients, therefore, 98 will be presented.

Complications are compared in Table I. The first column in this table includes 36 patients treated by vagotomy alone who have not yet required secondary gastric surgery. The second column includes 28 patients treated by vagotomy with simultaneous pyloroplasty, exclusion, or gastrojejunostomy. The third column includes 10 patients treated by vagotomy alone for gastroenterostomy stomal ulcers. The fourth column includes 12 patients requiring secondary pyloroplasty, exclusion, or gastrojejunostomy after treatment of duodenal ulcer by transthoracic vagotomy alone. The fifth column includes 9 patients with stomal ulcer occurring after subtotal resection and treated by vagotomy, 1 patient with duodenal ulcer treated by simultaneous subtotal resection and subdiaphragmatic vagotomy, 1 patient treated by subtotal resection for persistent duodenal ulcer following transthoracic vagotomy alone, and the 1 patient treated by secondary resection following vagotomy for gastric ulcer.

Major complications (Table I, A) have been described in previous reports and will not be discussed in detail. The operative mortality occurred in a patient treated by simultaneous transthoracic vagotomy and transabdominal drainage, a procedure now abandoned.

Persistence of ulcer, recurrence of ulcer, recurrence of ulcer, and intussusception were complications recognized in a few of a group of patients complain-

TABLE I. COMPLICATIONS OF VAGOTOMY GROUPED ACCORDING TO OPERATIVE PROCEDURE*

	VAGOTOMY ALONE (36 PATIENTS)	VAGOTOMY AND CONCURRENT DRAINAGE (28 PATIENTS)	VAGOTOMY AND PREVIOUS DRAINAGE (10 PATIENTS)	VAGOTOMY AND SECONDARY DRAINAGE (12 PATIENTS)	VAGOTOMY AND RESECTION (12 PATIENTS)
A. Major complications:					
Operative mortality	0	1	0	0	0
Persistence of ulcer	1	0	0	0	0
Recurrence of ulcer	1	0	0	0	0
Intussusception	1	0	0	0	1
Unexplained severe abdominal pain	4	0	1	3	0
Continuous severe diarrhea	0	0	1	1	3
B. Minor complications:					
Atypical ulcer-like symptoms	6	0	0	0	0
Bowel cramps or "gas pains"	18	9	2	7	7
Discomfort after eating	8	8	2	8	7
Discomfort several hours after eating	5	6	2	3	7
Mild periodic diarrhea	11	6	2	0	2

*Table includes patients who had duodenal or stomal ulcer but omits those who had gastric ulcer.

ing of abdominal pain. Diagnosis in others of this group was not possible. Episodes of acute abdominal pain necessitating emergency admission to the hospital in 6 patients were described in an earlier study.[5] Altogether, including these 6, there are 12 such problems which have been encountered. It was eventually demonstrated that 1 patient of the 12 had persistence of a duodenal ulcer, another a penetrating ulcer, and 2 intussusception.

Careful study has not determined adequate explanation for attacks of pain occurring in the remaining 8. Single attacks of pain occurred in 4 patients, three, ten, eighteen, and twenty-eight months, respectively, after vagotomy. Each attack subsided spontaneously and has not since recurred. In another patient several attacks occurred during a two-year period, each also subsiding spontaneously. Attacks in a sixth patient occurred every few weeks. Adequate explanation could not be found during repeated admissions to the hospital and during two exploratory operations. Symptoms subsided spontaneously twenty-four months after vagotomy.

The remaining 2 patients with abdominal pain presented different symptoms. In 1, twenty-one months after vagotomy and secondary drainage, a complaint of boring epigastric pain persisted. Neither splanchnic block nor spinal anesthesia relieved this pain. Control of medication for pain has been a problem. The second patient described less intense pain not relieved by splanchnic block. This continued one year. During the next year diarrhea was the major complaint. Medication for pain was also a problem.

It is evident (Table I) that these 8 unexplained pain problems occurred among 4 of 36 patients treated by vagotomy alone, 3 of 12 patients receiving secondary drainage late after vagotomy, and in 1 of 10 patients treated for stomal ulcer occurring after previous gastroenterostomy. No pain problem occurred in patients treated for duodenal ulcer by concurrent vagotomy and gastroenterostomy.

Continuous diarrhea was a major problem in 5 patients (Table I). Two had had gastroenterostomy. One treated for stomal ulcer occurring after gastroenterostomy developed diarrhea before vagotomy. This patient, previously described, died two years after vagotomy. The other was treated first for duodenal ulcer by vagotomy alone. Retention developed. Dietary treatment supplemented by use of Urecholine was then continued seven months. At this time pyloroplasty was performed but it only partially relieved retention. Episodes of diarrhea with ten to fifteen stools a day then occurred. These episodes lasted one week or ten days and recurred regularly after intervals of several days during which stools were less frequent but soft. This situation persisted for twelve months. Weight fell to twenty pounds below "normal weight."

Three patients with serious diarrhea had both vagotomy and resection. Of these, 2 stated that the diarrhea followed resection and became only moderately worse after vagotomy. One, a year after subtotal resection for gastric ulcer persisting after vagotomy, described six to eight stools, each of several days a week; weight at this time was fifteen pounds below what it was before the operations and thirty pounds below normal. The other had diarrhea three years between the time of subtotal resection and the time of vagotomy for

stomal ulcer; ten months after vagotomy this patient described eight to sixteen soft or watery movements each day. Weight was twenty pounds below that preceding resection. The third patient had not had diarrhea following resection. Twenty-eight months after vagotomy he reported six or more stools a day and was six pounds below what his weight had been before vagotomy.

Treatment employing conventional medicinal and dietary measures and also Urecholine and pancreatin was of little benefit in these 5 patients. Emotional problems present in each were not amenable to treatment. It is of interest that serious diarrhea did not develop among patients treated by vagotomy alone or by vagotomy and simultaneous drainage (Table I, A).

Atypical mild ulcer-like distress was described by 6 of 37 patients with duodenal ulcer treated by vagotomy alone (Table I, B). Epigastric distress was described as resembling that before vagotomy but much less intense. It occurred every several months, lasted a few days, and then subsided spontaneously. Occurrence of distress, in 2 at least, followed intemperate use of alcohol.

Mild or moderately severe bowel cramps, "gas pains," or bowel colic were experienced occasionally by 43 of the 98 patients discussed in this section (Table I, B). Incidence of "gas pains" was more frequent among patients requiring secondary drainage, 7 of 12, and among patients with vagotomy and resection, also 7 of 12. Most patients considered this complaint of minor importance. Only a few listed it as a cause of dissatisfaction.

The "dumping syndrome"* has been described as occurring after vagotomy and gastroenterostomy. All of our patients, therefore, were asked whether they now experience discomforts or abnormal sensations such as fullness, weakness, sweating, or pain immediately after eating. The 33 affirmative answers are tabulated in Table I, B. Incidence was equally frequent among patients treated by vagotomy alone, most of whom had delayed emptying of the stomach, and among patients with concurrent or previous gastroenterostomy, most of whom had prompt gastric emptying. Incidence was, however, higher in those who had secondary gastroenterostomy late after vagotomy and in those with vagotomy and subtotal gastric resection. In 3 instances this symptom was sufficiently serious to cause the patient to lie down or rest after meals.

Weakness associated with moderate sweating and, in one instance at least, mental confusion were described by occasional vagotomized patients as occurring long after eating or during the night. By questionnaire, therefore, each patient was asked whether discomforts or abnormal sensations such as weakness, sweating, or faintness were experienced when the stomach was empty as, for example, at 5:00 P.M. or during night or early morning. It is evident from answers enumerated in Table I, B that incidence was high only in the group with vagotomy and resection, 7 among 12. Since hypoglycemia might produce these symptoms, patients were asked whether taking food or candy relieved them. Of the total of 23 patients describing this symptom, 11 answered in the affirmative.

*The term "dumping syndrome" is conventionally applied to discomforts such as weakness, sweating, and epigastric discomfort experienced immediately after eating by patients with gastroenterostomy or subtotal resection.

Mild periodic diarrhea was described by 11 of 36 patients with vagotomy alone and by fewer patients in the other groups (Table I, B). Mild diarrhea or looseness of stools usually occurred every few weeks, lasted several days, and consisted of three to five soft or watery stools daily. Several additional patients stated that periodic diarrhea had occurred during the first several months after vagotomy and then ceased.

Other complications or side effects of vagotomy described in our last report[1] will be mentioned. During the first several weeks after operation one-third of the patients noticed temporary difficulty in swallowing. Evidently constriction or edema of the esophagus at the operative site caused obstruction. Difficulty in swallowing necessitated admission to the hospital of 3, who recovered spontaneously, and did not require dilatation of the esophagus. Malodorous regurgitations, foul eructations, and excessive flatus also occurred frequently. As time following vagotomy lengthened these symptoms decreased. Since gastroenterostomy has been routinely added to vagotomy, fewer patients have described these symptoms.

LABORATORY TESTS

The preceding section has dealt largely with subjective phenomena dependent upon statements of patients. This section will present objective evidence of results of vagotomy obtained by roentgenologic examination, aspiration of gastric secretions, introduction of balloons into the stomach, and determination of sugar content of venous blood. Outline form will be used since coauthors will later report detailed studies. Methods and technical limitations have been presented in a previous report.[5]

Roentgenologic examinations of the stomach after ingestion of barium have been conducted before and at monthly or yearly intervals as long as four years after vagotomy. Observations in the 7 patients treated for gastric ulcer will be presented first.

Before vagotomy, roentgenologic study revealed a juxta-esophageal crater 2½ cm. in diameter in 1 patient. After vagotomy and pyloroplasty this was not visualized during several examinations over an eight-month period. Study in another revealed a high, lesser curvature crater 3 cm. in diameter before vagotomy alone. Five months later it was again visualized only slightly smaller. A subtotal resection was then performed. Histologic examination of the specimen confirmed original diagnosis of benign gastric ulcer. Roentgenologic examination of a third patient before vagotomy alone revealed a crater of the antrum 3 cm. in diameter. This was not visualized during examinations 12 and 108 days afterward. One year later, however, a crater 1½ cm. in diameter was again visualized. After forty-eight days it could not be demonstrated. Study of a fourth patient before vagotomy alone revealed a high lesser curvature crater 2½ cm. in diameter. Postoperatively three consecutive examinations within eighty-seven days revealed healing leaving an hourglass contracture. The remaining 3 patients had prepyloric lesions. Examination in 2 revealed spasm and abnormal radiation of rugae. A small crater was visualized in the third. Consecutive examinations since vagotomy alone in 2 and vagotomy and pyloroplasty in the third failed to demonstrate crater.

Each of the 7 patients had active peristalsis before vagotomy and slow, sluggish, or apparently ineffectual peristalsis afterward. Emptying of the stomach was prompt before vagotomy. It was also prompt afterward in the patient with hourglass contracture and in 1 patient with vagotomy and pyloroplasty. Retention of barium six hours after ingestion varied from 25 to 100 per cent in the remaining patients.

Roentgenologic examination of the 9 patients with stomal ulcer occurring after subtotal gastric resection revealed craters in 5. Operation proved presence of ulcer in the remaining 4. At no time after vagotomy has examination demonstrated a crater. Since the antrum and most of the media of each stomach was missing, litle or no peristalsis could be demonstrated before or after vagotomy. Barium left the stomach promptly before and after vagotomy in 8 patients. In one, 30 per cent six-hour retention of barium developed after operation.

Results of preoperative and consecutive postoperative roentgenologic examinations of 36 patients treated for duodenal ulcer by vagotomy alone are summarized in Table II, A. For convenience, results in 46 patients with vagotomy and previous, concurrent, or secondary gastroenterostomy are grouped together and presented in Table II, B. Two patients, one inadequately followed, and 1 with an incomplete record are not included in this table. Also, not included is any reference to presence of deformity or crater. Examinations usually demonstrated deformity and frequently crater before vagotomy. Crater could be demonstrated afterward only in the 1 patient with persistence of a duodenal ulcer following vagotomy alone. Demonstration of the ulcer site was usually difficult following vagotomy because of poor emptying of barium from the stomach or because of deformity caused by pyloroplasty.

TABLE II. ROENTGENOLOGIC OBSERVATIONS

	BEFORE VAGOTOMY	AFTER VAGOTOMY		
	NO. OF PATIENTS	2 WEEKS TO 3 MO.	3 MO. TO 2 YR.	2 TO 4 YR.
A. Vagotomy Alone				
Patients tested	36	32	26	10
Peristalsis				
Active	36	1	2	0
Sluggish	0	31	24	10
6 hr. retention				
<30 per cent	36	12	11	5
>30 per cent	0	20	15	5
Size of stomach				
Normal range	30	6	6	5
Enlarged	6	26	20	5
B. Vagotomy and Gastroenterostomy*				
Patients tested	46	45	35	3
Peristalsis				
Active	39	3	3	0
Sluggish	7	42	32	3
6 hr. retention				
<30 per cent	39	27	31	3
>30 per cent	7	18	4	0
Size of stomach				
Normal range	25	21	25	3
Enlarged	21	24	10	0

*Table includes patients with previous, concurrent, or secondary gastroenterostomy.

Changes of motility, retention, and size of the stomach have been presented in Table II using arbitrary terms. "Active peristalsis" refers to observation of normal or excessive contractions. "Sluggish peristalsis" refers to peristalsis described by the fluoroscopist as being absent, slow, sluggish, or only fair. "Six-hour retention" refers to presence in the stomach of barium six hours after ingestion. Patients have been divided and listed arbitrarily as having less than or more than 30 per cent retention six hours after ingestion of barium as demonstrated by roentgenograms. Size of the stomach has been reported as within "normal range" or "enlarged." Enlargement refers to definite increase in size of more than 1½ times that preoperatively or 1½ times the usual size of the stomach of normal patients.

Peristalsis normal or hyperactive in most patients before vagotomy alone afterward became abnormal and usually sluggish (Table II, A). This change persisted in patients studied after two to four years. Active peristalsis when observed after vagotomy alone consisted of deep waves that progressed slowly. Forceful effective antral contractions seldom occurred. Thirty per cent or more retention at six hours usually occurred soon after vagotomy alone (Table II, B). Retention at six hours was often 70 to 95 per cent. Also, enlargement of the stomach usually occurred. As time following vagotomy lengthened, however, the number of patients having and not having retention and enlargement became more equal. Study of consecutive x-ray plates in 10 of these patients followed two to four years revealed that size of the stomach returned toward normal in 5, retention decreased in 4 and peristalsis remained slow and sluggish or only fairly active in all. In no instance has our roentgenologist (G. J. B.) observed peristalsis after vagotomy like that before vagotomy.

Patients treated by vagotomy and gastroenterostomy (Table II, B), also persisted with abnormal peristalsis. Retention and enlargement were often present during the first three months after operation. Subsequently, most had no retention and size of stomach was usually normal. Enlargement occurred and persisted in a few but did not exceed 1½ or 2 times normal size.

Roentgenologic examinations of small intestine and colon have been conducted in many patients before and at intervals after vagotomy, obtaining roentgenograms each hour for six hours. Before vagotomy abnormalities were observed in some patients. Afterward results of study varied. Usually transit through the jejunum was delayed, caliber increased slightly, and mucosal pattern tended to become coarser. Occasionally, excessive dilatation of loops of jejunum were observed. Abnormality of the colon was not observed.

Secretions from the stomach after fasting, insulin hypoglycemia, histamine, or ingestion of caffeine have been examined before and at intervals after vagotomy. Acidity of fasting secretions are presented in Table III. Patients are arbitrarily divided into groups having no free acid, some but less than 30 clinical units, and more than 30 units. Free acid usually exceeded 30 clinical units before vagotomy. Afterward this occurred in only a few patients even after two to four years. The two patients with more than 30 units two to four years after vagotomy had similar high values for free acid during the first two years. Secretions containing no free acid were obtained most frequently from patients

treated by vagotomy and gastroenterostomy (Table III, B). With few exceptions, volume of overnight twelve-hour collections of gastric juice was reduced one-half or more after vagotomy. These results indicate some reduction of gastric secretion. Nevertheless, calculation of combined and total acid indicates

TABLE III. ACIDITY OF FASTING GASTRIC CONTENT

	BEFORE VAGOTOMY	AFTER VAGOTOMY		
	NO. OF PATIENTS	2 WEEKS TO 3 MO.	3 MO. TO 2 YR.	2 TO 4 YR.
A. Vagotomy Alone				
Patients tested	33	32	25	8
No free HCl	0	18	10	3
Free acid less than 30 units	5	11	13	3
Free acid more than 30 units	28	3	2	2
B. Vagotomy and Gastroenterostomy*				
Patients tested	42	41	30	3
No free HCl	2	26	21	1
Free acid less than 30 units	15	10	9	2
Free acid more than 30 units	25	5	0	0

*Table includes patients with previous, concurrent, and secondary gastroenterostomy.

increased neutralization. Values for total acid before and after vagotomy were compared in 27 patients treated for duodenal ulcer by vagotomy alone. Amount decreased in 1, did not change in 12, and increased in 14.

Effect of intravenous administration of 15 or 20 units of insulin upon free acid of gastric secretion is abstracted in Table IV. Each test was run five hours. With few exceptions blood sugar was reduced to 50 mg. or less during the first hour. Numerous small variations of values for free acid occurred. For the table, therefore, a change of 25 units or less was arbitrarily considered not significant. Increases of more than 25 units occurred rarely after transthoracic vagotomy alone or after subdiaphragmatic vagotomy and drainage. Of 8 patients treated by vagotomy alone and followed two to four years, 4 had less and 4 more than 25 units of free acid. The 4 with positive tests had less than 25 units in tests performed during the first months and up to one and one-half years after vagotomy. Higher acid responses occurred only after two or three years. Similarly of two patients with vagotomy and drainage tested two to four years after vagotomy the 1 exhibiting high acid after insulin had no acid during a test three months after operation.

Gastric secretions have been examined before and after intramuscular administration of .5 mg. of histamine. Of 20 patients with duodenal ulcer tested before vagotomy alone, the amount of free acid increased more than 20 clinical units in 15. Of 26 patients tested after vagotomy alone, free acid increased more than 20 units in 11.

Caffeine test meals were given to 11 patients before vagotomy. Free acid increased more than 25 units in 8. Twenty-one patients were given caffeine test meals after vagotomy. Free acid in 15 did not change, or increased less than 25 units. Insulin tests in each of 9 of these patients tested were negative. Free acid increased more than 25 units in six. Insulin tests in 3 of 4 of these patients tested were positive.

TABLE IV. ACIDITY DURING INSULIN TEST*

	BEFORE VAGOTOMY	AFTER VAGOTOMY		
	NO. OF PATIENTS	2 WEEKS TO 3 MO.	3 MO. TO 2 YR.	2 TO 4 YR.
A. Vagotomy Alone				
Number of patients tested	5	17	15	8
Negative				
No free acid before or during test	0	7	3	1
No free acid before, increase of less than 25 units after	0	1	3	0
Free acid before, decrease, no change or increase of less than 25 units	1	7	7	3
Total negative	1	15	13	4
Positive				
No free acid before, increase of more than 25 units	2	2	2	3
Free acid before, increase of more than 25 units after	2	0	0	1
Total positive	4	2	2	4
B. Vagotomy and Gastroenterostomy				
Number of patients tested	5	24	27	3
Negative				
No free acid before or during test	0	9	11	1
No free acid before, increase of less than 25 units after	0	3	9	0
Free acid before, decrease, no change or increase of less than 25 units	4	8	5	0
Total negative	4	20	25	1
Positive				
No free acid before, increase of more than 25 units	0	2	1	1
Free acid before, increase of more than 25 units	1	2	1	1
Total positive	1	4	2	2

*Highest value for free acid during 6 hours after i.v. insulin is compared with value of control fasting specimens. Variations of less than 25 units of free acid have not been considered significant.

Gastrometric studies were performed before and at intervals after vagotomy in 56 patients. Intragastric balloons were routinely inflated to a volume of 300 c.c. using 50 c.c. increments of air. Intragastric pressure was recorded using a bromoform manometer. Results previously published[5] have been confirmed. Resting intragastric pressure or "tone" increased moderately and strong fluctuations of intragastric pressure, "peristalsis," decreased markedly or ceased. Eleven patients now have been followed two to four years. Resting intragastric pressure remained slightly increased and strong fluctuations of pressure "peristalsis" have not returned. Roentgenologic study revealed that balloons inflated to 300 c.c. usually lie in the media and fundus of the stomach. Increase of resting intragastric pressure or "tone" after vagotomy has been further con-

firmed in 6 patients using fluoroscopy and roentgenograms to control emptiness of the stomach and position of the balloon. One of us (E. J. L.), has gradually inflated balloons from 50 c.c. to 1000 c.c. in 4 patients before and after vagotomy. Resting "tone" after vagotomy further increases with larger volumes. Fluctuations of pressure low after vagotomy increase slightly at greater volumes but do not approach height at similar volumes before operation.

Gastrometric studies in one patient were most interesting. Operation was performed by a resident doing his first unsupervised vagotomy. Unlike other postvagotomy gastrometric studies, forceful fluctuations of intragastric pressure were present one week after operation. These persisted three months later. This patient after vagotomy also had large twelve-hour collections of gastric secretions with high free acid. Also, two insulin tests after vagotomy produced high free acid.

Blood Sugar.—Because patients occasionally complained of weakness between meals or during the night, fasting blood sugars taken prior to insulin tests before and after vagotomy have been compared. Before vagotomy alone the range was 91 to 105 mg. per cubic centimeter average 98. Two weeks to three months after vagotomy the range was 65 to 137, average 97. Three months to two years afterward, the range was 60 to 108, average 89. At two to four years, fasting blood sugars in 3 patients were, respectively, 100, 112, and 139. Other combinations of vagotomy; that is, vagotomy and drainage, vagotomy and resection, similarly had minor variations of blood sugar. Not included in these averages are 3 patients witih single unexplained pre-insulin blood sugar values of 193, 206, and 230 mg., respectively, after operation. Also, not included is the 1 patient developing definite diabetes after vagotomy and drainage requiring insulin to control blood sugar and glycosuria.

SPECIAL OBSERVATIONS

Persistence or recurrence of duodenal ulcer occurred in 2 patients treated by vagotomy alone. Each had high free acid in secretions from the fasting stomach. Also, volume of overnight collections of gastric content was large. Insulin hypoglycemia tests in one showed a change of pH from 1.55 before insulin hypoglycemia to 1.08 three and one-half hours afterward. Change in the other was from a pH of 2.8 before insulin to a pH of 1.5 two and one-half hours afterward. In one patient during the first months after vagotomy roentgenologic study revealed enlargement of the stomach to twice normal size, 50 per cent retention at six hours, and slow peristalsis of low amplitude. Symptoms of ulcer persisted. Fifteen months later barium emptied slowly out of a normal-sized stomach and a duodenal crater was demonstrated. Roentgenologic study in the other patient at the time of recurrence nine months after vagotomy revealed a normal-sized stomach with feeble peristalsis and 50 per cent retention at six hours. Duodenal ulcer was demonstrated at operation. Gastrometric studies in one of these patients after vagotomy revealed no fluctuations of intragastric pressure. Free acid was present in fasting secretions of each of 6 additional patients treated by vagotomy alone for duodenal ulcer and then during the first two years afterward experiencing temporary recurrence of ulcer-like symptoms.

The 3 patients with recurrence or persistence of gastric ulcer after vagotomy each had little or no acid in fasting secretions. Two had moderate retention by x-ray. One tested had a negative response to insulin hypoglycemia. The one patient who developed a gastric ulcer four months after vagotomy alone for duodenal ulcer had acidity values for fasting secretions varying from a pH of 1.65 to pH of 1.95. A caffeine test meal produced only slight increase of free acid. Eighty per cent six-hour retention of barium and enlargement of the stomach to three times normal had been present soon after vagotomy and peristalsis was sluggish.

Adequate observations of motility and acidity during intervals between vagotomy and drainage and after drainage were obtained in 8 of 10 patients requiring gastroenterostomy for retention occurring after transthoracic vagotomy alone. Between vagotomy and drainage, retention, as judged by barium in the stomach 6 hours after ingestion, ranged from 70 to 100%. Size of the stomach varied from one and one-half to four times normal. Peristalsis was sluggish or absent. After gastroenterostomy 6 patients had no retention and 3 had 5, 10, and 40 per cent, respectively, stomachs being normal in size. Peristalsis varied from sluggish and slow to only fair. Between vagotomy and drainage some free acid was present in fasting gastric secretions of 4 patients, 4 having no free acid. After drainage 7 patients had no free acid, only 1 having values as high as before, pH 1.3 to 1.45.

Urecholine (urethane of B-methyl choline)* has been used frequently since October, 1946. During the first week or ten days after vagotomy it was routinely administered intramuscularly† and along with prolonged gastric suction, delayed feeding, and nightly residual aspirations it apparently aided emptying of the stomach. Also, 36 patients took Urecholine orally‡ after vagotomy for periods varying from several weeks to nine months. Most experienced complete or partial relief from symptoms such as fullness after eating and bowel cramps. Intermittent or periodic mild diarrhea only occasionally diminished. Patients with continuing severe diarrhea, however, failed to respond to Urecholine as also to acid orally, sulfasuxidine, or pancreatin. More detailed observations concerning use of urecholine have been presented[1] and are reported separately.

Vagotomy has been used for 3 patients in addition to the 104 reported in this paper. Each suffered with intractable pain from an ulcerating lesion of the stomach. One had an inoperable carcinoma invading the pancreas. Another had actinomycosis extensively involving the stomach and associated with multiple small liver abscesses. The third had an ulcerating lesion of the stomach associated with thoracic and abdominal lymphadenopathy apparently caused by Boeck's sarcoid. In each patient gastric resection or celiac ganglionectomy seemed contraindicated and vagotomy was tried. Immediate relief of pain occured and persisted six months to one and one-half years.

Intussusception occurred in 2 of the 104 patients treated by vagotomy. Each was treated because of recurring episodes of pain before and after operative reduction. The first complained of attacks of cramping abdominal pain several

*Supplied by Merck & Co., Inc., Rahway, N. J.
†Urecholine 2.5 mg. subcutaneously every four hours during the day.
‡Urecholine 30 mg. before breakfast and 15 mg. midmorning and midafternoon.

months before reduction. Pain disappeared spontaneously after most attacks, was partially relieved by Urecholine during others, and was once relieved by splanchnic block. After operation mild attacks recurred but were relieved by Urecholine. These have since ceased.

The second patient was admited to the hospital three times before reduction. Relief from pain occurred spontaneously once, after spinal anesthetic another time, and after tetraethylammonium chloride the third. Each time pain recurred within several weeks. Exploratory operation and operative reduction were carried out during the fourth admission. Two weeks later the patient again returned with pain. This time it was relieved by Dibutoline (dibutyl-urethane of dimethyl-ethyl-beta-hydroxyethyl ammonium sulfate).* Recurrences continued until eighteen months after the first exploration and were at times associated with melena. Another exploration was then performed and three areas of intussusception were present in the same segment of proximal jejunum. Two feet of this bowel were resected.

DISCUSSION

The 104 patients with peptic ulcer described here have each presented symptoms or findings currently acceptable as indications for subtotal or total gastric resection. Patients have not been selected except that some were referred because resection had failed. Most were chronic invalids. Although vagotomy or vagotomy and drainage have occasionally produced complications, we believe that considering the type of patients treated rate of rehabilitation has been respectably high. Mortality rate has been reassuringly low.

Explanation for and treatment of some complications have been evolved. Others respond to Urecholine or Dibutoline. Likelihood of occurrence of complications is evidently decreased by combining subdiaphragmatic vagotomy with some form of gastroenterostomy. Experience is not yet sufficiently great to warrant comparison of pyloroplasty, exclusion, or gastrojejunostomy as drainage procedures. However, we now use a short loop posterior gastroenterostomy with a small stoma routinely. It is our present belief that better methods of diagnosis and treatment of complications will be necessary before vagotomy can be considered a standard surgical method of treatment of peptic ulcer.

Also, it is our belief that duration of effects of vagotomy cannot yet be properly evaluated. Usually after transthoracic or transabdominal vagotomy, reduction of volume and acidity of gastric secretions and of propulsive force of gastric motility occurs and persists. Exceptions cannot be correlated with acid responses to insulin hypoglycemia. Nevertheless, acid responses to insulin hypoglycemia became more frequent in patients followed two to four years after vagotomy. Initial acid responses could be attributed to overlooked nerve fibers and later recovery of acid response to nerve regeneration. Available evidence does not warrant criticizing of this interpretation. It does warrant statement that definite so-called "positive" insulin tests are not frequent among patients with high free acid in fasting secretions or with recurrence of ulcer. It seems probable that some chemical or mechanical factor not dependent upon presence

*Supplied by Merck & Co., Inc., Rahway, N. J.

of the vagus nerves influences acidity of gastric secretions after vagotomy. It is also of interest that usually after vagotomy the amount of combined acid increases as free acid decreases. This would indicate increased neutralization of acid.

The exact mechanism for relief of pain has not been determined. Available evidence indicates that visceral afferents conducting pain do not travel through the vagus nerves. It is, therefore, of interest that 3 patients with painful gastric lesions of known etiology other than that of peptic ulcer were relieved of pain following vagotomy.

Although it is as yet too early to predict the future of vagotomy as a surgical treatment for all forms of intractable peptic ulcer, it appears to us that continuation of use of the procedure is warranted, that difficulties have been reduced, and that results after two to four years are encouraging.

CONCLUSION

1. Major complications such as postoperative ulcer, severe pain or diarrhea, and intussusception after vagotomy have occurred most frequently following vagotomy without gastroenterostomy or following vagotomy in patients who also had subtotal gastric resection. They have occurred least frequently after vagotomy and concurrent drainage.

2. Minor complications such as atypical ulcer-like symptoms, bowel cramps, discomfort after eating, and mild periodic diarrhea occurred in some patients after vagotomy and gastroenterostomy but were most frequent in the groups that had vagotomy alone or vagotomy and resection.

3. Effects of vagotomy on gastric motility and on acidity of fasting secretions have usually persisted during observation periods up to four years. A few patients, however, have developed high free acid responses to insulin hypoglycemia years after vagotomy.

4. Persistence or recurrence of duodenal ulcer following vagotomy occurred in patients having high free acid in fasting gastric secretions.

5. Secondary gastroenterostomy with one exception decreased amount of free acid in gastric secretions.

6. Vagotomy relieved pain in 3 patients with ulcerating lesions of the stomach, 1 caused by carcinoma, 1 by actinomycosis, and 1 by Boeck's sarcoid.

REFERENCES

1. Grimson, K. S., Rundles, R. W., Baylin, G. J., Taylor, H. M., and Linberg, E. J.: Vagotomy —Clinical Experiences During Four Years, J. A. M. A. **139**: 508-513, 1949.
2. Dragstedt, L. R., and Owens, F. M.: Supra-diaphragmatic Section of the Vagus Nerves in Treatment of Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **53**: 152-154, 1943.
3. Grimson, K. S., Taylor, H. M., Trent, J. C., Wilson, D. A., and Hill, H. C.: The Effect of Transthoracic Vagotomy Upon the Functions of the Stomach and Upon the Early Clinical Course of Patients With Peptic Ulcer, South M. J. **39**: 460-472, 1946.
4. Moore, F. D., Chapman, W. P., Schulz, M. D., and Jones, C. M.: Transdiaphragmatic Resection of the Vagus Nerves for Peptic Ulcer, New England J. Med. **234**: 241-251, 1946.
5. Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. M., and Rundles, R. W.: Transthoracic Vagotomy, J. A. M. A. **134**: 925-932, 1947.

THE NECESSITY FOR TRACHEOTOMY IN THE TREATMENT OF TETANUS TO PREVENT LETHAL RESPIRATORY COMPLICATIONS

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ACCORDING to the Bureau of Vital Statistics there were 585 deaths from tetanus in the United States in 1946. In Louisiana alone 37 deaths were recorded in the same year. Since Vinnard,[1] in November, 1944, reported 352 patients treated in the previous ten years, 184 additional patients have been admitted to the Charity Hospital of Louisiana, of which 65 (34.7 per cent) succumbed. A mortality rate of 35 per cent in a condition which is preventable is indeed a reflection on the American public and the profession for not having universal prophylactic immunization. During World War II the experiences of the American[2] and British[3] Armies demonstrated that active immunization practically eliminated tetanus.

In 1927 Ramon[4] showed that active immunity to tetanus resulted from inoculation with formalized toxin; yet today, twenty-two years later, no large scale attempt at active immunization has been carried out exclusive of the military personnel. Indeed, passive immunity by means of tetanus antitoxin is all too frequently neglected in the treatment of unimmunized injured patients. Many pediatricians now employ the combination of pertussis vaccine with diphtheria and tetanus toxoid in infant immunizations[5] but until this type of practice is generally adopted no appreciable reduction in the incidence of tetanus will be realized. In spite of a better understanding of the pathologic physiology of the disease and effective means of producing active and passive immunity, tetanus remains a common and frequently fatal disease among the civilian population.

It has been demonstrated that if a lethal dose of tetanus toxin becomes fixed and altered by the central nervous system, treatment is of no avail.[6] Sublethal doses of toxin produce a clinical complex which runs a variable course depending upon the ability of the patient and his physician to cope with attendant problems of respiratory obstruction, pulmonary infection, cardiac and renal failure, and disturbances in nutrition and fluid balance. No specific countermeasure is at hand for attacking the altered toxin; therefore, the only real hope for reducing the mortality is in the improvement of supportive therapy and the prevention of complications.

With extensive experience with tetanus at Charity Hospital a routine plan of management has been evolved with the gradual reduction of the death rate as shown by the reports of Gessner and Adiger,[7] Graffagnino and Davidson,[8]

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Graves,[9] Boyce and McFetridge,[10] and Vinnard.[1] With further improvement in the curative treatment of tetanus we have been able to decrease materially the mortality rate in tetanus although the recent number of patients treated is small. In the six-month period from July 1 to December 31, 1948, eight patients with severe tetanus were admitted to the Tulane Surgical Service of Charity Hospital. Five patients recovered, two died shortly after admission before therapy could be instituted, and in only one, in whom death occurred on the ninth hospital day, could the treatment be considered a failure. In the management of these patients several changes in our therapy were developed.

DIAGNOSIS

Generally the diagnosis is not difficult. Headache, stiffness of the neck muscles, and difficulty in swallowing in a patient who has had recent injury are sufficient to justify a diagnosis of tetanus. The more severe symptoms and signs of trismus, opisthotonos, abdominal rigidity, dysphagia, and convulsions permit no error. A wound or history of injury is usually found but neither is necessary for establishing the diagnosis. A trial of conservative therapy in suspected tetanus is indefensible and at least the initial phase of treatment should be begun on suspicion of the disease.

TREATMENT

The course of the disease in tetanus varies considerably in different patients. In one instance respiratory tract infection may dominate the picture; in another, cardiac or renal failure can occur and represent even greater problems than the tetanus itself; in all, the effects of the toxin must be ameliorated and adequate food and fluid intake provided.

The treatment is divided into two phases: (1) the initial treatment and (2) the maintenance of the patient and prevention and treatment of complications. The former consists of those measures which are instituted immediately upon making a diagnosis of tetanus or suspecting it. The latter will vary somewhat depending upon the manifestations and severity of the disease. On the Tulane Surgical Service the supervision of these cases is made the responsibility of one resident who from the time of admission directs their management. Finally, the sine qua non of any successful therapeutic program depends upon experienced nursing care which is provided on a round-the-clock basis.

Initial Treatment

1. *History and Physical.*—Every effort should be made to obtain an accurate history of the disease. The date and type of injury and date and sequence of symptoms are especially important regarding prognosis. As a rule a short incubation period is associated with a high mortality rate but not invariably so. In examining the patient one should determine the type of operative care needed for treatment of the wound of entry and the status of the cardiorespiratory systems. A thorough neurologic examination is imperative when the patient is first seen so that the progress of the disease may be followed.

2. *Tetanus Antitoxin.*—After skin testing for sensitivity the patient is given 50,000 units of tetanus antitoxin intramuscularly, and another 50,000 units diluted with 300 to 500 c.c. of 5 per cent dextrose in distilled water intravenously. It is important to neutralize any free circulating toxin at the earliest opportunity.

3. *Operative Therapy.*—All patients with a wound or history of having had a wound even though it is healed must have wound excision. We have found the usual preoperative doses of morphine and atropine are sufficient for control in this early period. Each patient is individualized and additional barbiturate is given if required. The resident anesthetist is consulted during this phase regarding the choice of drugs for sedation, control of spasm, and operative anesthetic.

Cyclopropane or ethylene with curare is the anesthetic of choice. Pentothal sodium is avoided because of the associated high incidence of laryngeal spasm. Local anesthesia is also not employed because the attendant manipulation and pain may provoke hyperactivity. The wound of entrance is excised completely to normal tissue and packed open with fine mesh gauze impregnated with fresh zinc peroxide paste. If the wound is large and on an extremity, a plaster splint is applied. At this time all patients with signs of severe tetanus should have a tracheotomy performed. This will be discussed in a later section. Following the operation the patient is returned to the observation ward where a darkened, quiet room and expert nursing care are available.

Maintenance and Management of the Patient

The patient is placed in a quiet, darkened, single room. Sideboards are placed on the bed to prevent falls. Oxygen, suction machine, and a Kreiselman resuscitator for artificial respiration are immediately available. In mild cases in which a tracheotomy has not been performed, a tracheotomy set should be immediately available should respiratory difficulty arise. In addition a Drinker respirator must be obtainable quickly should it be required.

1. *Tetanus Antitoxin.*—Provided wound excision has been adequate there is probably no rational physiologic basis for the continued administration of tetanus antitoxin. However, we usually administer from 5,000 units to 25,000 units daily intramuscularly for five days. Local and intrathecal antitoxin have not been used.

2. *Sedation.*—Sedation of the tetanus patient is aimed at reducing irritability, diminishing muscle spasm, and controlling convulsive seizures. No single agent has been found which will safely accomplish these objectives.

For the past five years at Charity Hospital the Department of Anesthesia* has supervised this aspect of the treatment of the tetanus patient. Many different drugs have been used, alone and in combination, in an attempt to find the agent best suited for this purpose. These drugs and the results obtained with each are as follows:

Avertin: Avertin has been used at Charity Hospital for the treatment of tetanus since 1930. The usual dose is 50 mg. per kilogram of body weight mixed

*Under the direction of Dr. John Adriani.

with 100 c.c. of distilled water instilled into the rectum. This dosage satisfactorily diminishes the hyperexcitability of the patient and reduces the frequency and severity of convulsions. With larger doses muscle spasm and convulsive seizures practically can be abolished but the profound depressant effect of such doses on the respiratory center prohibits their use. Further, in the stuporous, uncooperative tetanus patient the Avertin solution is frequently expelled after a short time so that the amount of the drug absorbed is purely speculative.

Barbiturates: The barbiturates also have had wide usage as sedatives in tetanus. Phenobarbital in doses ranging from 2 to 4 gr. every four to six hours has satisfactorily controlled the restless excitement of most patients. Sodium amytal and sodium pentothal intravenously are useful during convulsive seizures in amounts which vary according to the response of the patient. Like Avertin, however, these agents when given in large doses at frequent intervals depress respiration and increase stupor, thus aggravating pulmonary complications.

Curare.—In 1947 Adriani and Ochsner[11] reported the use of curare (aqueous solution) in five cases of tetanus. A dosage of one-half unit per pound of body weight was used. As a result of their experience they felt that the use of curare in the treatment of tetanus was hazardous. Its trial in additional cases since that report has served to support this conclusion. The action of the drug is of short duration (approximately 40 minutes) and repeated doses are necessary at frequent intervals to maintain the desired effect. Moreover, in order to secure muscle relaxation complete curarization with its characteristic respiratory and, occasionally, cardiac failure is necessary. We no longer use the aqueous solution of curare in treating tetanus.

Procaine hydrochloride: Following the report of Graubard and Ritter[12] on the use of intravenous procaine in the treatment of posttraumatic pain and edema an effort was made to determine its usefulness in tetanus. Reasoning that its action on both sensory nerve endings and motor end plates might alleviate the pain and muscle spasm it was given to patients in 0.1 per cent solution. One gram of procaine dissolved in 1,000 c.c. normal saline solution was given intravenously at a rate best tolerated by the patient during which time careful records of the blood pressure, pulse, and respiration were kept. It was found that procaine intravenously did abolish pain and diminish muscle spasm but in this dosage the central excitation was often so marked as to require intravenous sodium pentothal to counteract it.

Procaine and Avertin: In view of the central stimulation accompanying the intravenous administration of procaine it was reasoned that perhaps larger, more effective doses of Avertin might safely be used if the two drugs were given simultaneously. Sixty milligrams of Avertin per kilogram of body weight were given rectally and at the same time an infusion of 0.1 per cent procaine was started. In twenty-two cases the results were gratifying. More complete muscle relaxation was achieved than with the smaller doses of Avertin, yet no evidence

of marked respiratory depression was noted. Although this method needs further clinical trial we feel that it may prove valuable in the handling of some patients with severe tetanus.

Curare in oil: In a recent report Weed and associates[13] reported satisfactory control of the convulsions and muscle spasm in tetanus with curare in wax and oil. At present the anesthesia department is employing this drug in cases of tetanus but in the several instances in which it has been used to date it is the consensus that there is little to recommend it. Its effects are still unpredictable, varying as they do with the same dosage.

Myonecine: This synthetic, curare-like drug is now under investigation by Adriani.[15] Given orally in 62.5 to 750 mg. doses every two to four hours, it has relieved muscle rigidity and spasm to a satisfactory degree. However, its value in severe tetanus has not yet been demonstrated.

In summary, none of these agents has been found capable consistently of relieving muscle spasm and convulsions safely. Sedation is given principally to reduce the restless excitability and to control the convulsive seizures. For this purpose our plan of sedation management is as follows: phenobarbital in 1½ to 2 gr. doses is given every six hours p.r.n. Avertin, 50 mg. per kilogram. is given rectally every twelve hours p.r.n., and sodium pentothal intravenously in the event convulsions occur. Under this regimen the tetanus patient becomes relatively quiet although tonic muscle spasm may persist. The excitability threshold is raised sufficiently so that the routine hospital activities do not disturb the patient. Pain does not seem to be an important factor once the fear of suffocation is alleviated by tracheotomy. In our experience trismus, stiffness of neck and abdominal muscles, and even moderate opisthotonos, do not in themselves influence the final outcome of the disease.

3. *Nutrition and Fluid Balance.*—All patients are fed by Levine tube if there is any evidence of trismus or dysphagia. The patient is heavily sedated before passage of the tube because otherwise the procedure will excite pharyngeal spasm. The tube feedings consist of a high carbohydrate—high protein mixture with vitamin supplements. Thus, a daily diet of 1,800 to 2,000 calories is provided. In addition, tap water is given by the tube to bring the daily fluid intake to 3,000 c.c. Whole blood is given as indicated. All patients have received one or more transfusions. Periodic determinations of the hematocrit, white blood cell count, blood urea nitrogen, serum chlorides, and serum proteins are done. The urine is examined on admission and thereafter as indicated. An indwelling urethral catheter is used to prevent urinary retention as well as to secure an accurate record of the urinary output. The latter is extremely important in elderly patients with concomitant renal or cardiac disease. During convalescence a high protein diet supplemented with vitamins and iron is provided and gradual return to activity is permitted.

4. *Avoidance of Respiratory Complications.*—Prevention of respiratory complications has been mentioned in discussing supportive treatment. All patients receive penicillin in doses ranging from 200,000 to 400,000 units daily.

Penicillin has no effect upon the disease itself[14] but its primary purpose is prophylaxis against respiratory complications. Long-acting preparations would be ideal but have not been available to us.

Of equal importance has been the elective use of tracheotomy. In all patients with any oral difficulty, either trismus or dysphagia, tracheotomy is performed on admission. Other cases are observed and if signs progress, tracheotomy is done. The heavily sedated patient being fed by Levine tube, barely able to move his jaws, unable to swallow, subject to pharyngeal and laryngeal spasms during which the airway is blocked, is certainly a candidate for tracheotomy. We are convinced that tracheotomy should be done *before* the need arises. At times it is a life-sustaining measure. In this series failure to use it caused one death. Almost as important as overcoming the suffocating effects of laryngeal spasm, tracheotomy permits aspiration of bronchial secretions which are particularly hazardous in the sedated patient by predisposing to atelectasis and pneumonitis. These are frequently the cause of death in tetanus. Tracheotomy provides a simple means of securing tracheobronchial toilet.

The following case histories are presented in order to illustrate some of the most important features of the treatment of tetanus.

CASE REPORTS

CASE 1.—B. L., a white girl, aged 8 years, was admitted July 9, 1948, with a history of a nail puncture wound of the right foot two days previously which had received no treatment. On admission she complained of lumbar backache and trismus, and opisthotonos rapidly developed. Examination revealed an extremely irritable child with marked trismus and opisthotonos. All reflexes were hyperactive. A diagnosis of tetanus was made and treatment instituted immediately. The patient was skin tested for sensitivity and 50,000 units of antitoxin were administered intramuscularly. Under general anesthesia (Vinethene) the wound of entrance was débrided widely and packed open with fine mesh gauze impregnated with fresh zinc peroxide paste. Upon admission to the observation ward because of the extreme degree of trismus, a tracheotomy was performed. Oxygen was given by tracheotomy catheter and a 300 c.c. infusion of normal saline solution containing 50,000 units of antitoxin was given. Under the direction of the department of anesthesia 0.1 per cent procaine was given intravenously. As soon as the patient was well relaxed a Levine tube was passed into the stomach and tube feedings, supplemented with tap water, were started. The admission x-ray of the chest revealed a bronchopneumonia in the right lung. Penicillin in doses of 25,000 units every three hours and full doses of sulfadiazine were given.

During the subsequent twenty-one days the temperature ranged between 101° and 103.6° F. and the pulse rate varied from 140 to 160. The child was irrational, restless, and had frequent convulsions. On several occasions artificial respiration was necessary. In addition bronchopneumonia developed in the left lung. It soon became apparent that sufficient procaine to control spasms could not be given safely so this drug was discontinued and Avertin 50 mg. per kilogram per rectum was used instead. At times the depressant effect of this agent was so great that it was discontinued and sodium amytal intravenously was given to control convulsions.

On the twenty-second day she improved. For the first time she became aware of her surroundings and thereafter rapidly returned to normal and was discharged on the forty-first hospital day.

Comments.—Several factors in the management of this severe case of tetanus are worthy of comment. Based upon our previous experiences because

of the early onset of symptoms and because of their severity the prognosis in this case at the outset was considered practically hopeless. Immediate tracheotomy appeared to be a lifesaving procedure even though there was no evidence of respiratory obstruction on admission. In the ensuing days tracheobronchial secretions formed constantly and in great quantities. With the tracheotomy it was relatively simple to remove, by aspiration of the trachea and larger bronchi, the abundant secretions, and it is our conviction that had this not been done the child would have succumbed. In spite of the extremely short incubation period (two days) the patient recovered. Sedation was never satisfactory and although during the first three weeks muscle spasm was not controlled satisfactorily, this did not seem to influence unfavorably the course.

CASE 2.—J. J., a 58-year-old colored man, was admitted Oct. 5, 1948, with a chief complaint of "locked jaws." Six days before admission slight trismus was first noticed. This progressed so that by the time the patient was admitted he had not been able to eat for three days and could open his mouth only ¼ to ½ inch. Shortly after the appearance of trismus he had noticed stiffness of the neck, shoulder, and back muscles which became progressively worse. For at least four months the patient had had an unhealed "sore" over the left tibia, the site of an old abrasion.

On examination marked trismus with risus sardonicus was present. Nuchal, abdominal, and back rigidity were severe. Reflexes were hyperactive. A 3 by 2 inch dirty ulcer was present over the left mid-tibia. Fifty thousand units of tetanus antitoxin were given intramuscularly in the accident department and on arrival in the observation ward an additional 50,000 units were given intravenously. Peripheral blood values were normal except for a leucocyte count of 13,500 with 78 per cent polymorphonuclears. Urinalysis and blood chemistry were normal. The patient was sedated with sodium phenobarbital 1 and atropine and taken to the operating room where the ulcer was widely excised under intravenous sodium pentothal and local procaine anesthesia. The wound was left open and dressed with fine mesh gauze impregnated with zinc peroxide paste. Simultaneously an elective tracheotomy was performed.

The patient reacted well without spasm. Sedation with luminal and Avertin was continued as required. On October 7 and October 8 intravenous procaine preceded by Avertin, 50 mg. per kilogram, were used. Twenty-five cubic centimeters of this 0.1 per cent procaine solution were used each time without effect on rigidity but with an increase in restlessness. Penicillin, 25,000 units every three hours, was given throughout the course of the disease. Tube feedings were employed. Tetanus antitoxin to a total of 190,000 units was given during the nine days following surgery.

During the night of October 17 the patient removed the Levine tube, which was replaced by the nurse. The next 6 ounce tube feeding was injected into the trachea. A widespread pneumonitis developed with copious secretions. The leucocyte count rose to 29,000. During the next ten days the temperature ranged between 101° and 104° F., not returning to normal until Nov. 9, 1948. Oxygen by tracheotomy catheter and multiple transfusions were used. The penicillin dosage was doubled and sulfadiazine given. During this period of severe aspiration pneumonia the effects of tetanus were steadily decreasing. By October 25 oral feedings were taken readily and the tracheotomy tube was removed on Nov. 11, 1948. The patient was then transferred to a general surgery ward for skin grafting of the excised wound.

Comment.—This represents a moderately severe case of tetanus accidentally complicated by aspiration pneumonia. The tracheotomy was indispensable for aspirating the copious secretions which followed the accidental introducing of a feeding into the trachea. We believe that local and sodium pentothal anes-

thesia should not have been used in this case although nothing untoward happened. Although no undesirable effects resulted from their use we believe that it was unwise to employ local analgesia and intravenous pentothal for the wound excision.

CASE 3.—W. D., a 42-year-old colored man, was admitted with chief complaint of tightening of the face and pain in the back. Five weeks before admission the patient suffered a crushing injury to the right forefoot. The skin was broken in several places with compound fractures of the first, second, and third toes. No tetanus antitoxin was given. The injury was treated with elevation, chemotherapy, and hot soaks by his insurance physician. The wound became malodorous and the foot swelled. The day before admission the patient noticed a tightness of the facial muscles with progressive dysphagia and the back felt stiff and painful.

On examination there was a typical risus sardonicus. The mouth could be opened only slightly. The deep reflexes were hyperactive. The neck and back muscles were moderately rigid. The abdomen was negative. The foot showed gangrene of the first, second, and third toes and there was an ulcer at the base of the first toe. The foot and ankle were swollen. The patient was given 3 gr. of phenobarbital hypodermically and 50,000 units of tetanus antitoxin intramuscularly shortly afterward in the observation ward. An additional 50,000 units of tetanus antitoxin were given intravenously in an infusion. The laboratory work was essentially negative. At surgery, four hours after admission, under cyclopropane anesthesia the forefoot was amputated through the distal third. The wound was left open and dressed with fine mesh gauze impregnated with fresh zinc peroxide paste. The patient withstood the procedure well.

During the first postoperative day an attempt was made to pass a Levine tube initiating a succession of spasms during which the patient arched in marked opisthotonos with obvious obstruction to respiration. Avertin, 6 c.c., was given rectally and expelled. Respiration ceased shortly and tracheotomy was done without effect. Artificial respiration was started and continued. Intracardiac adrenalin was given with immediate return of the heartbeat. Shortly thereafter gasping, labored respirations began and eventually became effective. The apnea lasted five to seven minutes during which time neither pulse nor blood pressure was obtainable and the tracheotomy wound did not bleed. Two hours after return of respiration severe spasms occurred necessitating sodium amytal intravenously. For the next twenty-four hours spasms were frequent but thereafter were absent except for a brief period on the ninth day. Sodium amytal intravenously in 3¾ gr. doses was sufficient for general irritability and restlessness. Consciousness was never regained after the period of anoxia.

Lower nephron syndrome followed the period of respiratory and circulatory collapse but by the fifth day the output had risen above 1,800 c.c. and thereafter was in that range, no true diuresis occurring. Generally, fluid equal to 1,500 c.c. plus the previous day's urinary output was given. Every other day 1,000 c.c. of this were given as normal saline solution. Early in the patient's hospital stay the blood urea nitrogen rose and the CO_2 combining power fell but later the patient was in electrolyte balance. The bulk of the fluid was given by Levine tube. An indwelling urethral catheter was used throughout.

Generalized rigidity was severe. The neck was stiff, abdominal and back muscles rigid. Arms and legs could be moved at the joints passively only with difficulty. Trismus was complete. Rigidity was more marked the morning of respiratory arrest and thereafter it was difficult to decide whether cerebral damage from anoxia or tetanus was accountable for the picture. The temperature rose quickly and ranged from 101° to 105° F. until just before death when it was 108°F. The patient did not develop pneumonia and the wound was under control after surgery. Penicillin, 400,000 units daily, was given from onset. Sulfadiazine in full doses was also given the last three days of the illness. Death resulted from respiratory arrest with markedly rising temperature. Clinically it was felt that cerebral damage was the primary cause of death.

Post-mortem revealed bilateral pleural effusion, bilateral acute pulmonary edema and congestion, cardiac hypertrophy, and mucopurulent tracheobronchitis. The brain was not examined.

Comment.—The long incubation period in this case suggested that the tetanus would be mild. Early tracheotomy might well have avoided the period of respiratory arrest as spasm did not produce respiratory obstruction after tracheotomy. If sedation had been given before attempting to pass the gastric tube, severe spasm would have been avoided. In spite of his poor condition renal failure was corrected within a period of four days and before death the patient was thought to be in electrolyte balance. This case represents a treatment failure since undoubtedly the fixed toxin was less than a full lethal dose.

CASE 4.—J. A. McC., a white girl aged 17 years, was admitted with a four-day history of trismus following an attack of tonsillitis of three days. She had been treated by her local physician without improvement. No history of injury was obtained although the supposition was that the tonsil was the portal of entry.

Examination revealed a marked risus sardonicus, trismus, opisthotonos, and rigidity of the abdominal muscles. Deep reflexes were hyperactive and twitchings of the legs were observed. The temperature was 100° F., pulse 140, and respirations 30. Laboratory determinations were normal with the exception of a moderate leucocytosis (15,400).

A diagnosis of tetanus was made and treatment instituted immediately. After skin testing, 50,000 units of antitoxin were given intramuscularly and 50,000 units intravenously in 1000 c.c. of normal saline solution. Because of cyanosis and respiratory difficulty a tracheotomy was performed and oxygen administered by means of tracheotomy catheter. Phenobarbital, 3 gr., had been given on admission. Thereafter under the supervision of the department of anesthesia Avertin, 50 mg. per kilogram, rectally, and phenobarbital, 2 gr., were used as needed to control spasms and restlessness. Usually these drugs were given only twice daily. After much difficulty a Levine tube was passed and feedings and fluid administered. In addition penicillin, 50,000 units every three hours, and tetanus antitoxin, 20,000 units daily for three days, were ordered. Tracheal aspiration was performed frequently because of copious secretions.

On the tenth hospital day there was evidence of improvement with relaxation of the jaw and neck muscles and clearing of the sensorium. From this point an improvement was rapid and the patient was discharged on the twenty-sixth hospital day.

Comments.—This case represents the favorable course of moderately severe tetanus when early tracheotomy and only moderate sedation were used to avoid pulmonary complications.

CASE 5.—F. J. (Charity Hospital No. 336814), a 40-year-old colored man, was admitted with a four-day history of pain in the back and legs and stiffness of the neck and back. Dysphagia had been present for one day and convulsions had appeared just prior to admission. Two weeks previously he had injured the right middle finger for which no treatment had been given.

Examination revealed a superficial purulent infection of the finger, dysphagia, opisthotonos, and spasm of the abdominal muscles but no trismus. Deep reflexes were hyperactive. A diagnosis of tetanus was made and treatment instituted. Phenobarbital, 3 gr., and 50,000 units of tetanus antitoxin were given intramuscularly. The local wound was débrided widely and packed open with fine mesh gauze impregnated with zinc peroxide. In the observation ward Avertin, 50 mg. per kilogram, was given rectally and an infusion of normal saline solution containing 50,000 units of tetanus antitoxin was started.

The patient could open the jaws widely but dysphagia was marked and opisthotonos and abdominal rigidity extreme. Because of the dysphagia a Levine tube was passed and feedings begun. On the fifth hospital day spasms which obstructed respiration became frequent

and tracheotomy was performed. Following tracheotomy the patient was easier to control and had a better mental outlook since during the spasms air could now be obtained and the patient's marked fear of suffocation was alleviated. Rigidity of the abdominal, neck, and back muscles plus trismus and dysphagia with occasional spasms remained unchanged until the tenth day, after which gradual recovery took place. Tube feedings were discontinued on that day and the tracheotomy cannula was removed twelve days after insertion. From admission to the twelfth hospital day the patient received 200,000 units of penicillin daily. During the early period relatively heavy doses of Avertin and phenobarbital were required. Intravenous procaine was used on one occasion without effect on muscle rigidity. During the first seven days after the initial treatment the patient was given a total of 165,000 units of tetanus antitoxin—25,000 units daily for five days and then 20,000 units daily for two days. The wound was treated with daily dressings with zinc peroxide and healed. The patient was discharged on the twenty-seventh hospital day without residual.

Comment.—At onset this case appeared quite severe with intermittent bouts of spasm during which the patient had considerable respiratory obstruction. After tracheotomy spasms did not obstruct respiration as they had before. The patient responded well to treatment. It would have been better judgment to have performed the tracheotomy on admission.

CASE 6.—M. S., a 41-year-old colored woman, was admitted with a history of having stuck a large splinter of wood into the right foot between the third and fourth toes fifteen days before. The foot became so swollen and painful that walking was impossible. Local application of sugar and soap did not improve the condition. On the third day after injury the wound began to exude a thin, bloody fluid and she felt feverish. Two days before admission she consulted a physician because of epigastric pain and difficulty in swallowing. He administered 3,000 units of tetanus antitoxin and 1.2 million units of penicillin and referred her to Charity Hospital.

When seen in the accident room her temperature was 101° F., pulse 140, and respirations 30. The abdominal muscles were rigid and deep reflexes hyperactive although no trismus or opisthotonos was present. The right foot was extremely swollen and in the web space between the third and fourth toes there was a small puncture wound exuding thin, serosanguineous, foul-smelling pus.

In the accident room 50,000 units of toxin-antitoxin were given intramuscularly. The patient was taken to the operating room, where, under pentothal and nitrous oxide anesthesia the wound was opened widely and débrided. In the depths of the wound a piece of lead pencil approximately ¾ inch long was found and removed. The wound was packed open with fine mesh gauze impregnated with zinc peroxide paste and the patient sent to the observation ward. Fifty thousand units of tetanus antitoxin were given intravenously in 500 c.c. of normal saline solution and a Levine tube was passed into the stomach for feeding. In addition, 25,000 units of penicillin every three hours and tetanus antitoxin, 25,000 units daily, were ordered. For sedation phenobarbital, 11 gr. every four hours, and Avertin, 50 mg. per kilogram rectally every twelve hours, were used when necessary.

On the second hospital day the patient exhibited trismus and moderate opisthotonos with slight nuchal rigidity. These signs progressed rapidly and respiratory obstruction became evident, which necessitated tracheotomy. Through the tracheotomy cannula oxygen was administered.

Following tracheotomy the patient's condition rapidly improved and by the eighth day practically all signs of muscle spasm had disappeared. She was discharged on the twenty-eighth day free of symptoms and with the wound of entry well healed.

Comments.—On admission this patient was thought to be suffering from relatively mild tetanus associated with a severe infection about the wound of entry. The rapid development of severe symptoms and signs of tetanus with

respiratory obstruction proved the error of our initial evaluation. However, the dramatic improvement following tracheotomy supports our conviction that it should be done routinely in all cases of severe tetanus.

DISCUSSION

Although considerable progress has been made in the treatment of tetanus, the mortality rate has remained prohibitively high. Prophylaxis is undoubtedly the most valuable method of therapy. Active immunization against tetanus has proved to be efficacious and it is hoped that in the not too distant future the entire population will be immunized. Another important prophylactic measure is wound excision at the initial treatment of an injury.

After the development of symptoms and signs of tetanus, which occurs only after toxin has been formed, has gained entrance to the blood stream, and a certain amount at least has been fixed by the central nervous system, the prognosis generally has been bad. Although wide excision of the wound and the administration of large amounts of antitetanic serum remove the source of infection and neutralize the free toxin, the persistence of manifestations due to the toxin already fixed in nerve tissue too frequently causes complications which are fatal.

Muscle irritability, spasm, and convulsions so dominate the clinical picture in tetanus that most therapeutic efforts have been directed toward their control. For this reason, profound sedation which is frequently necessary to control muscle irritability has been used. In spite of the prevention of convulsions by heavy sedation and probably partly because of the undesirable effects of sedation on respiratory function, the mortality rate has remained high. It was hoped that the relaxing action of curare might beneficially affect the course of tetanus but this has not proved to be so because of the narrow margin of safety between the therapeutic and toxic doses.

In analyzing fatal cases of tetanus we have been progressively impressed with the high incidences of respiratory complications which were apparently responsible for the fatal outcome. Because of the beneficial effects of tracheotomy performed in a severe case of tetanus complicated by bronchopneumonia in a child 8 years of age we became convinced that many fatal complications of tetanus could be prevented by overcoming any respiratory difficulty by early tracheotomy. Although at first this appears as a radical procedure it is in fact a very conservative one because not only does it eliminate practically all respiratory embarrassment by maintaining an open airway, but it also greatly facilitates the removal of tracheal and bronchial secretions. Moreover, we have become progressively more convinced that profound sedation which otherwise is so harmful by predisposing to respiratory complications is not necessary if an open airway is maintained. Although undoubtedly some patients with tetanus still will succumb, most can be saved by the prompt performance of a tracheotomy because death in tetanus is due largely to pulmonary complications which can be prevented by maintenance of an adequate airway.

REFERENCES

1. Vinnard, R. T.: Three Hundred Fifty-Two Cases of Tetanus, SURGERY **18**: 482, 1945.
2. Glenn, F.: Tetanus—A Preventable Disease, Ann. Surg. **124**: 1030, 1946.
3. Boyd, J. S. K.: Epidemiology and Statistics, Lancet **1**: 113-119, 1946.
4. Ramon, G., and Zoeller, Chr.: L'Anatoxine Tétonique et L'Immunization Active de L'Homme vis-a-vis du Tetanos, Ann. de l'Inst. Pasteur **41**: 803-833, 1927.
5. Hamilton, P. M., and Knauf, E. G.: Combined Immunization Against Diphtheria, Tetanus, and Pertussis, J. Pediat. **25**: 236-238, 1944.
6. Firor, W. M.: Treatment and Prevention of Tetanus, Surg., Gynec. & Obst. **75**: 185 (Internat. Abstr. Surg.), 1943.
7. Gessner, H. B., and Adiger, D.: Treatment of Tetanus, New Orleans M. & S. J. **69**: 91, 1916.
8. Graffagnino, P., and Davidson, J. M.: Tetanus, New Orleans M. & S. J. **76**: 311, 1924.
9. Graves, A. M.: Tetanus in New Orleans, Ann. Surg. **92**: 1025, 1930.
10. Boyce, F. F., and McFetridge, Elizabeth M.: Analysis of 185 Cases of Tetanus from the New Orleans Charity Hospital, New Orleans M. & S. J. **87**: 825, 1935.
11. Adriani, J., and Ochsner, A.: Some Observations on the Use of Curare in the Treatment of Tetanus, SURGERY **22**: 509-515, 1947.
12. Graubard, D. J., and Ritter, H. R.: Intravenous Procaine in the Treatment of Trauma, Am. J. Surg. **74**: 765-769, 1947.
13. Weed, M. R., Purvis, D. F., and Warnke, R. D.: D-Tubocurarine for Control of Spasm in Tetanus, J. A. M. A. **138**: 1087, 1948.
14. Altemeir, W.: Penicillin in Tetanus, J. A. M. A. **130**: 67-72, 1946.
15. Adriani, J.: Personal Communication.

A DOUBLE LUMEN INTRATRACHEAL TUBE FOR SIMULTANEOUS OXYGEN ADMINISTRATION AND TRACHEOBRONCHIAL ASPIRATION

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MAINTENANCE of an adequate airway and the value of oxygen therapy postoperatively need not be stressed. Many patients with heart and lung diseases examined at necropsy are found to have collections of thick, mucoid secretions in the tracheobronchial tree which could account for the immediate cause of death. The ominous death rattle of bubbling mucus is nothing more than secretions in the larger airways which the patient is unable to expel. In order to prevent these collections of thick mucoid secretions and insure adequate oxygen, a new type of tube† has been developed which is inserted in the trachea or main stem bronchus and allowed to remain for long periods of time. The double lumen of the tube permits simultaneous oxygen administration and either continuous or intermittent aspiration of the tracheobronchial tree. The tube is useful in the postoperative patient and particularly in any comatose or semicomatose patient who is unable to expel tracheobronchial secretions and who is in need of oxygen.

THE TUBE

The tube (Fig. 1) is 20 French caliber. The suction lumen is 5 mm. wide and the oxygen lumen is 3 mm. wide. The distal 10 cm. has a molded curve which is modeled after the Magill endotracheal tube. This facilitates introduction of the tube through the glottis, and aids in exact placement in either main stem bronchus, as will be described later. There is a longitudinal line extending from the tip on the concave side of the curve which aids in placing the tube in the trachea through the glottis but is invaluable in orientation of the tip when introducing it in either main stem bronchus. There are two transverse markers. The first one, 18 cm. from the beveled tip, indicates the approximate distance of the glottis from the nares. The second marker, 32 cm. from the beveled tip, represents the approximate distance of the carina from the nares.

Prior to manufacture of the specially designed tube described here, a portion of a Miller-Abbott double lumen intestinal tube was used for simultaneous aspiration and oxygen administration of the tracheobronchial tree. However, the small lumen frequently precluded aspiration of the thick, viscous secretions.

ADDITIONAL EQUIPMENT

Oxygen is administered from a tank or a pipe line with a suitable regulator, flow meter, and humidifier. I feel that it is important to have the

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†Manufactured by George P. Pilling & Son Co., Philadelphia, Pa.

oxygen humidified. Any suction device may be employed to withdraw the secretion from the tracheobronchial tree. Fig. 2 illustrates tube in place with necessary equipment.

INDICATIONS FOR USE OF TUBE

The use of a catheter for aspirating the tracheobronchial tree is not new. Haight and Ransom[1] described the intratracheal suction methods in the prevention of atelectasis and bronchopneumonia in the postoperative patient.

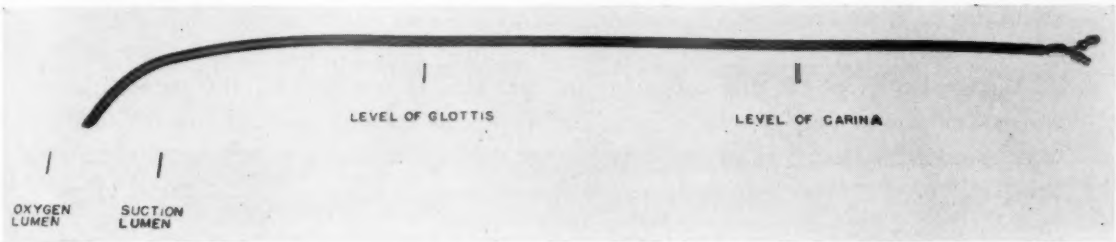


Fig. 1.—Double lumen intratracheal tube with curved distal end. First marker indicates the level of the glottis; second marker indicates level of carina. The longitudinal line runs along the concavity of the tube, aiding in ih the introduction of the distal end in either main stem bronchus.

Fig. 2.—Endotracheal tube in place, with large lumen connected to suction machine, and smaller lumen connected to oxygen supply.

Foregger[2] emphasized the value of this procedure, demonstrating clearly how endotracheal intubation may be a lifesaving procedure and stated that an endotracheal tube may be left in place for a long period of time without harmful results. It has been suggested by Dripps[3] that a theoretical objection to the small catheter for tracheal aspiration is the possibility that alveolar gases may be withdrawn by suction as the vocal cords close around the aspirating

catheter. This objection has been met by employing the double lumen tube, just described, so that simultaneous oxygen administration may be accomplished with either intermittent or continuous suction of the pulmonary tree. Indications for the use of oxygen in surgery have been carefully reviewed by Kisner[4] and he also suggests giving 7 per cent carbon dioxide with the oxygen.

Intratracheal suction, which was continuous, was first used quite accidentally, upon a postoperative chest patient at the Pennsylvania Hospital, Philadelphia, in 1945. Following resection of a carcinoma of the esophagus, a Levine tube was supposedly introduced in the esophagus and suction applied as well as intranasal oxygen. A routine chest film twenty-four hours later demonstrated that the tube was in the trachea. On removal, the patient developed obvious collections of tracheobronchial secretions which previously had been aspirated. In retrospect it was felt that the continuous suction of the trachea had been beneficial in maintaining a clear airway, and no ill effect was observed during its use with nasal oxygen.

I also used catheter suction on the neurosurgical ward at Brooke General Hospital, Fort Sam Houston, Texas. It was observed that pulmonary complications were the most common cause of death in the comatose patient or in the patient who failed to regain consciousness immediately postoperatively. When these patients were aspirated with a catheter introduced in the trachea, cyanosis frequently developed. Cyanosis did not develop when simultaneous oxygen was administered. At necropsy the lungs showed little evidence of congestion and no ecchymosis or ulceration of the mucous membrane was evident after prolonged intubation.

In patients who have had general anesthesia the tube seems particularly useful for simultaneous oxygen administration and tracheal suction until the patient fully reacts. Thus, in the important initial postoperative period the patient is assured of sufficient oxygen and maintenance of a clear airway.

Recently the tube has been employed on patients in the medical wards who are comatose and unable to expel secretions. In other patients in whom pulmonary transudates have accumulated following trauma, accidental or operative, with development of the so-called "wet lung,"[5] the dyspnea may be relieved and fluid removed by use of the indwelling double lumen tube.

TECHNIQUE OF INTUBATION

The actual technique of passage of an intratracheal tube is familiar to the anesthetist and bronchoscopist, but the average intern or resident has little training or experience in passing endotracheal tubes, and considers blind passage a formidable procedure.

In reality, blind passage, using a few simple precautions can be accomplished even in the comatose patient.[6] Cocaine or pontocaine is used to anesthetize and shrink the mucous membrane of the nasal mucosa and nasopharynx. The tube, which is lubricated with Nupercaine ointment, is then inserted gently and smoothly through the inferior meatus. As the pharynx is approached, the head is tilted backward or extended. It is this positioning

that, in my experience (Fig. 3) is important in passage of the tube into the trachea, although Magill[7] recommended that the mandible should be held at right angles to the cervical spine. The maneuver seems to open the glottis and the esophagus cannot be entered with ease. In contrast, the head, when sharply flexed, will usually result in the tube entering the esophagus because the epiglottis covers the tracheal opening. Thus, by carefully positioning the head, a tube can be introduced at will in either the esophagus or trachea. Some manipulation of the tube is frequently necessary if the tube is too far lateral and impinging against the pyriform fossa, or if it is too far anterior and resting upon the anterior commissure. The longitudinal line indicates the concavity of the curve at the distal end which aids in guiding the beveled tip into the trachea through the vocal cords.

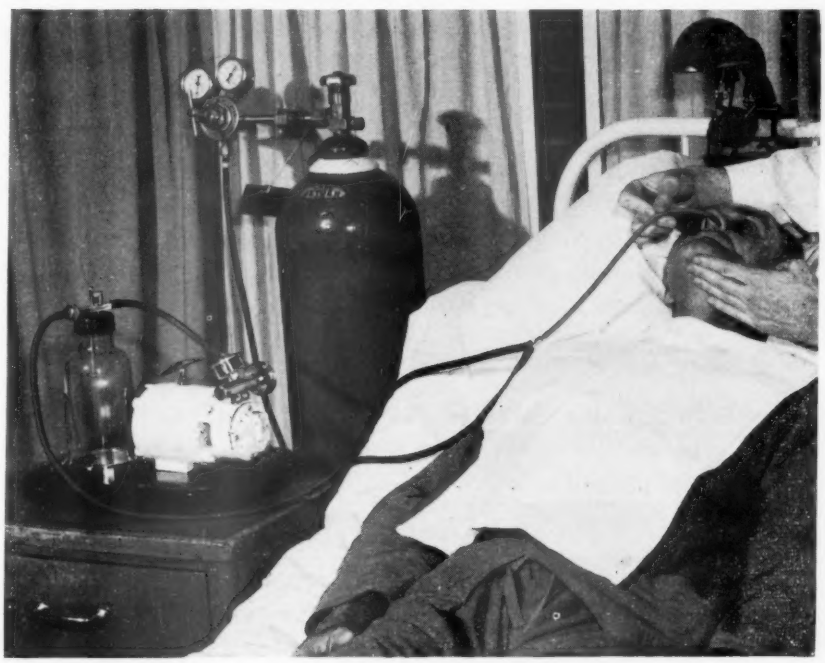


Fig. 3.—Technique of passage of double lumen endotracheal tube. The head is hyperextended, which seems to aid in blind introduction through glottis into trachea.

Markers on the tube indicate (Fig. 1), as previously mentioned, the approximate sites of the vocal cords and carina. Ideally, the end of the tube when in place should lie between the cricoid cartilage and the bifurcation of the trachea. The proper length to be inserted can be measured by laying the tube longside the patient's neck. The trachea bifurcates at the angle of Louis and the beveled end measured from the nares to this point will determine the point of the carina in relation to the tube markers.

Since the level of the carina can be established in relation to the markers on the tube, the carina can be stimulated and produce a definite activation of the cough reflex, even in the comatose patient. Secretions are thus removed from the bronchioles despite the fact the distal end does not reach these finer air passages.

If aspiration of one or the other of the main stem bronchi is desired, the curve is directed toward this lung by rotating the tube using the longitudinal line as an indicator of the direction of the concavity at the distal end. The right main stem bronchus usually can be entered with ease, but due to the more acuteness of the angle more precise manipulation must be done to enter the left bronchus.

Figs. 4, *B* and 5 show the tube in the right and left main stem bronchus, respectively.

At times the suction lumen may become clogged with thick, viscid secretions. It may not be necessary to withdraw the tube in order to dislodge the plug because temporarily changing the oxygen flow to the suction side will open the lumen. However, in cases in which the tube is allowed to remain endotracheally for long periods of time, it is recommended that routine removal and cleaning be performed every twelve to twenty-four hours.

OXYGEN ADMINISTRATION

Experience has shown that usually 6 liters of oxygen per minute are sufficient to maintain adequate oxygenation. However, it has been suggested[8] that only by direct experiment can the amount of oxygen needed be determined. The most reliable physical signs are pulse and color, and repeated observations will indicate whether flow is adequate.

CASE REPORTS

The double lumen tube has been used in approximately 60 cases at this hospital. The tube with the curved tip described here has been employed in 15 medical and surgical patients.

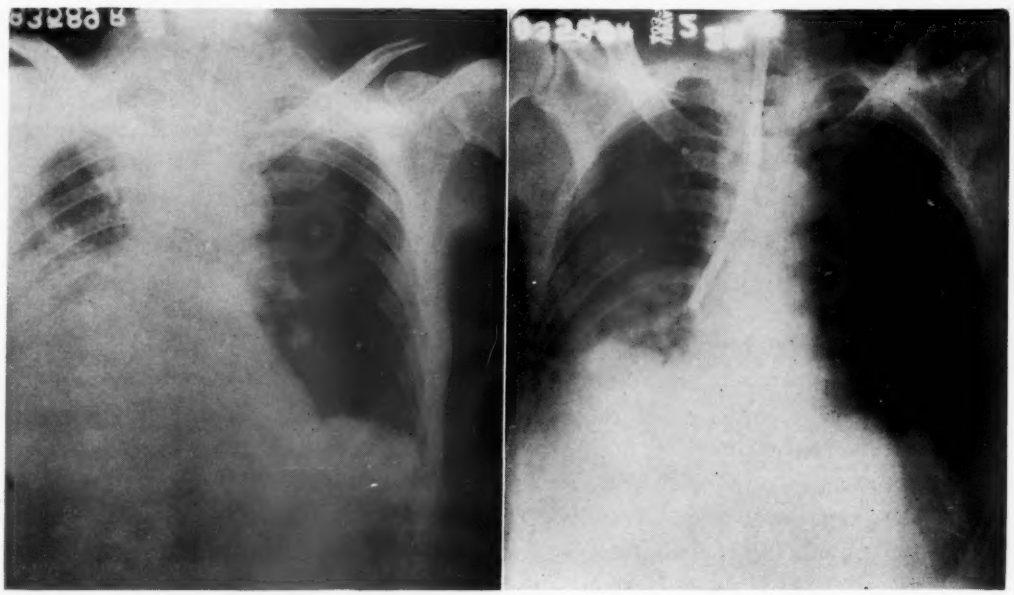
CASE 1.—A 56-year-old man was subjected to a total gastric resection for what later proved to be a chronic ulcer, benign, of the lesser curvature. On the seventh postoperative day the patient developed bronchial breathing, dullness, and shift of the trachea on the right side. Temperature spiked to 101° F. Roentgenogram (Fig. 4, *A*) showed massive atelectasis with shift of the mediastinum to the involved right side. The double lumen tube was inserted and a tremendous amount of thick, foul-smelling sputum was obtained. The tube was inserted daily and allowed to remain in place for several hours each day for three days until x-ray and physical signs indicated the right side of the chest to be clear. Fig. 4, *B* shows the tube in the right main bronchus and some residual basilar atelectasis on the day following the initial episode.

Comment.—This patient developed a typical postoperative atelectasis and was treated successfully by the double lumen endotracheal tube. He was treated on the ward, and the tube was introduced daily until clinical and x-ray signs demonstrated the chest was clear.

CASE 2.—A 70-year-old man had numerous admissions to the medical service because of diabetes mellitus, cerebral thrombosis, and generalized arteriosclerosis. He was again admitted for acidosis, vomiting, and cardiorespiratory complaints. Ten days after admission the patient became comatose, developing many coarse râles in the left side of the chest and some signs of pulmonary edema. When the patient was unable to expel collections of secretions in the tracheobronchial tree the double lumen tube was introduced in the left main bronchus (Fig. 5) with immediate improvement in color and gradual disappearance of the

coarse râles. The tube was allowed to remain in place for three days, during which time the patient had short periods of consciousness. On the fourth day the patient died of what was interpreted to be a cardiac and renal death. No post-mortem examination was permitted.

Comment.—This patient illustrates the use of the tube in a semicomatose medical patient who is unable to expel the tracheobronchial secretions. The



A. *B.*

Fig. 4 (Case 1).—*A*, Typical massive atelectasis in postoperative gastrectomy patient. Tube is in trachea and suction has been started. *B*, X-ray view with tube in right main stem bronchus, showing effect of aspiration of thick viscous secretions.

Fig. 5 (Case 2).—Roentgenogram demonstrates tube in left main bronchus in semicomatose medical patient. Tube was allowed to remain in place three days, during which time patient received 100 per cent oxygen and frequent aspirations.

tube was placed blindly in the left main bronchus and allowed to remain in place for three days with continuous oxygen and intermittent suction as indicated.

CASE 3.—A 54-year-old man, a neurosurgical patient, underwent craniotomy for a brain tumor. The tumor was inoperable and postoperatively the patient failed to respond. When obvious audible râles developed in the trachea, associated with cyanosis, continuous oxygen and intermittent suction were instituted by means of the double lumen tube. The tube was inserted twice daily and allowed to remain in place for two to four hours, which was adequate to maintain a clear tracheobronchial tree. The patient was fed by means of a stomach tube and remained alive for twenty-nine days in spite of the comatose condition. Post-mortem examination showed very little fluid or secretions in the main bronchi and no ulceration or edema was noted of the trachea or glottis, as a result of the tube.

Comment.—In this unconscious neurosurgical patient the tracheobronchial toilet was maintained by use of the double lumen tube for twenty-nine days.

COMPLICATIONS

The use of an indwelling tube for long periods of time would appear to have certain hazards. The damage caused to tracheal mucosa and vocal cords is certainly to be considered. However, the trachea and vocal cords have been inspected at post-mortem examination of patients in whom the tube has been in place for as long as six days, and no ulceration or even unusual hyperemia have been demonstrated. Lundy[9] felt that any complication that develops following prolonged intubation is due more to the trauma of introduction rather than to the presence of the tube lying in the trachea. He warned, however, of the potential danger of introducing organisms foreign to the patients by careless cleansing and intubation.

Gillespie[6] in an excellent discussion of prolonged intubation quoted cases in which a tube remained in place for as long as twelve days with no evidence of damage to cords, larynx, or trachea. He cited two important considerations which should be observed when an endotracheal tube remains in place: (1) Liquids must be carefully administered for they may be easily aspirated since the cords do not close tightly; (2) the tube should be changed every twelve hours and cleaned because of dried mucous collections.

The double lumen of the tube prevents positive intrabronchial pressure developing from oxygen administration. The pressure, if allowed to develop, could possibly cause emphysema and hinder the return of blood to the heart.[6]

Precautions must be taken to prevent fire and explosion when high concentrations of oxygen are used with open electric suction machines.

Some alert patients object to the discomfort of the indwelling tube. While probably its greatest usefulness is in the comatose or slowly reacting postoperative patient, intubation can be accomplished easily in the conscious patient. Again, the simple precaution of adequately anesthetizing the mucous membrane with local anesthesia should be observed. Chest and neurosurgical patients who normally must be sedated with great care to avoid dulling the cough reflex, can safely receive more narcotics since the tracheobronchial secretions are aspirated.

SUMMARY

1. A double lumen intratracheal tube is described for the simultaneous administration of oxygen deep in the tracheobronchial tree, and the aspiration of secretions.

2. It is applicable in the patient who is in need of oxygen and who cannot adequately expel the tracheobronchial secretions. Particular indications include any patient with atelectasis, the postoperative chest and neurosurgical patient, and the semicomatose or comatose medical patient.

3. A simple method of introduction by blind passage through the nose is described. Cumbersome apparatus for oxygen administration is not necessary. The only equipment needed is local anesthesia (cocaine or pontocaine), oxygen tank, humidifier, and portable suction apparatus.

4. The tube is not only useful in intermittent aspiration but may be left in the trachea as an indwelling endotracheal tube as long as secretions must be removed and concomitant oxygen therapy is indicated.

REFERENCES

1. Haight, Cameron, and Ransom, Henry K.: Observations on the Prevention and Treatment of Postoperative Atelectasis and Bronchopneumonia, Ann. Surg. **114:** 243-258, 1941.
2. Foregger, Richard: The Value of Endotracheal Intubation, J. A. M. A. **133:** 1200-1201, 1947.
3. Dripps, Robert D., and Deming, Margery N.: Postoperative Atelectasis and Pneumonia, Ann. Surg. **124:** 94-110, 1946.
4. Kisner, Wendell H.: Oxygen Therapy in Surgery, Am. J. Surg. **76:** 76-82, 1948.
5. Daniel, Rolin A., Jr., and Cate, William R., Jr.: Wet Lung—An Experimental Study, Ann. Surg. **127:** 836-857, 1948.
6. Gillespie, Noel A.: Endotracheal Anesthesia, ed. 2, Madison, Wis., 1948, University of Wisconsin Press.
7. Magill, I. W.: Endotracheal Anesthesia, Am. J. Surg. **34:** 450-455, 1936.
8. Fundamentals of Anesthesia. Subcommittee on Anesthesia, National Research Council. Ed. 2, Chicago, 1944, American Medical Association.
9. Lundy, John S.: Clinical Anesthesia, Philadelphia, 1942, W. B. Saunders Company.

A TECHNIQUE FOR EXTENSIVE THORACOLUMBAR SYMPATHECTOMY WITHOUT RIB RESECTION

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SINCE the surgical treatment of hypertension was first proposed in 1923,[1] a number of operative procedures have been devised to achieve this objective. The first effective procedure, anterior rhizotomy,[2] was soon replaced by subdiaphragmatic splanchnicectomy.[3] In 1935, Peet[4] introduced supradiaphragmatic sympathectomy and splanchnicectomy by a retropleural approach. The operation which now bears his name is performed in one stage through a paravertebral incision followed by the removal of the medial portion of the eleventh rib. The lowest three thoracic sympathetic ganglia are removed along with adjacent segments of the splanchnic nerves.

Dissatisfied with his results from the supradiaphragmatic operation, Smithwick[5] devised a two-stage procedure in which the sympathetic chain was approached both below and above the diaphragm. Originally he excised part of the twelfth rib, incised the diaphragm, and by a retropleural approach removed the splanchnic and sympathetic nerves from the ninth thoracic to the second lumbar ganglion inclusive. Subsequently he modified this procedure to include resection of the twelfth and part of the eleventh rib.

In 1941, Grimson[6] described an operative technique for total paravertebral sympathectomy. This three-stage procedure involves two incisions on each side of the thorax and a fifth incision in the midline of the abdomen. Segments of the third and tenth rib are removed, but the approach to the sympathetic nerve trunks is transpleural and transperitoneal. This operation is more effective in lowering blood pressure than the Smithwick procedure, but the greater mortality and morbidity associated with so formidable an operation have prevented its widespread adoption; therefore, various compromises have been devised. In four such procedures advocated, respectively, by Hinton,[7] Poppen,[8] Goetz,[9] and White[10] a retropleural approach is used, while Linton[10, 11] prefers a transpleural route. All involve the resection of one or more ribs.

Of the various modifications of the Smithwick operation, we used that of Hinton for some time but encountered certain difficulties which appeared to be inherent in this procedure.

(1) After the resection of the ninth or tenth rib, we were confronted with the problem of separating a very thin and tense parietal pleura from

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the endothoracic fascia. Consequently, rents in the pleura were the rule rather than the exception. When the parietal pleura remained intact, an extrapleural pneumothorax was produced.

(2) The exposure of the thoracic sympathetic and splanchnic nerves necessitated an extensive separation of the pleura from the chest wall. This trauma to the pleura seemed to be the chief cause of a rather profuse serosanguineous effusion which often appeared twenty-four to forty-eight hours after operation.

(3) During the closure of the thoracotomy the air was removed from the chest cavity by inflation of the lung under positive pressure while suction was applied to a large catheter in the incision. Not infrequently the mobilized pleura exerted a valvelike action, sealed the opening in the catheter, and prevented evacuation of air from the pleural cavity and the extrapleural space. In some instances there was enough residual pneumothorax after operation to produce dyspnea, relieved only by pleural aspiration.

(4) The resection of a rib not only added to the trauma of the procedure but seemed to be associated with a high incidence of postoperative intercostal neuralgia. This incidence was not appreciably reduced by resection of the intercostal nerve associated with the resected rib or by the injection of procaine into the adjacent intercostal nerves.

These technical difficulties seemed inherent in any operative procedure in which an extensive thoracolumbar sympathectomy would be performed by rib resection and a retropleural approach. On the other hand Weinberg and Kraus[12] recently reported a series of 109 consecutive cases in which the intercostal incision was used for a wide variety of thoracic operations including pneumonectomy, pulmonary decortication, transthoracic vagotomy, and transdiaphragmatic gastrectomy. Weinberg[13] suggested that it might well be feasible to use an intercostal approach without rib resection for thoracolumbar sympathectomy. Accordingly, the following operative technique was evolved.

TECHNIQUE

The patient is placed in a lateral position on the operating table. The hip joint on the side of the operation is extended in order to tense the psoas muscle. The table is flexed with the apex of the break midway between the lowest rib and the iliac crest to facilitate exposure of the lumbar sympathetic chain. (See Fig. 1.)

An incision is made in the ninth interspace extending forward about 20 cm. from the costal angle. A portion of the latissimus dorsi is divided and the external oblique and serratus anterior are split in the direction of their fibers. The intercostal muscles and parietal pleura are incised parallel to and exactly midway between the ribs. Insertion of the left index finger into the pleural cavity as soon as the latter has been opened provides an accurate guide to the midline of the interspace (Fig. 2). When the intercostal incision has been completed, the ribs are separated gradually by a Finochietto retractor. The great splanchnic nerve and the sympathetic chain, covered by the parietal

pleura, are readily identified on the lower thoracic vertebrae. The pleura is incised longitudinally, midway between the sympathetic and great splanchnic nerve trunks (Fig. 3).

The incision in the pleura is carried down to the diaphragm, which is incised for a distance of 10 cm. parallel to and 3 cm. from the costal attachment. Here, likewise, the left index finger provides a useful guide so that the peritoneal cavity will not be entered (Fig. 4). The kidney presents through the diaphragmatic incision and is examined at this stage for gross evidence of disease. A renal biopsy may be taken. The adrenal gland is readily palpated.

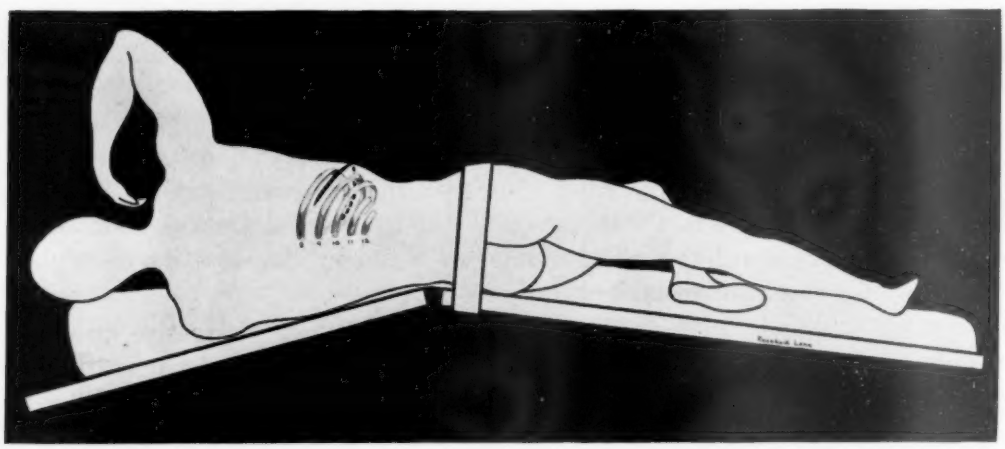


Fig. 1.—Position of the patient on the operating table. The incision is shown in the eighth interspace. This incision is used when an especially high level of sympathectomy is desired, but ordinarily it is less satisfactory for the lumbar part of the operation than the approach through the ninth interspace, described in the text.

Next the kidney in its fatty capsule is retracted forward exposing the psoas muscle, which is cleared of its loose areolar covering. The large first lumbar ganglion is easily identified at this stage and is mobilized by cutting its communicating rami (Fig. 5). The dissection is carried caudalward until the second lumbar sympathetic ganglion has also been mobilized. A silver dura clip is placed on the chain distal to that ganglion as an x-ray marker, and the nerve is severed just proximal to the clip. The dissection of the sympathetic chain is then carried cephalad, mobilizing the roots of the various splanchnic nerves as they are reached. When the sympathetic trunk has been freed to the level of the origin of the uppermost splanchnic root, the dissection of the splanchnic nerves is completed, and they are severed at the level of the upper margin of the semilunar ganglion.

The cutting of the splanchnic nerves is thus deferred until the sympathectomy is almost complete because of the sharp drop in the blood pressure which usually follows splanchnic section. In order partly to counteract this sudden marked hypotension, the break in the operating table is removed and the patient is placed in a moderate Trendelenburg position. The mobilization of the upper thoracic sympathetic ganglia is then completed (Fig. 6). The upper level of sympathectomy varies from the fifth to the second thoracic

Fig. 2.

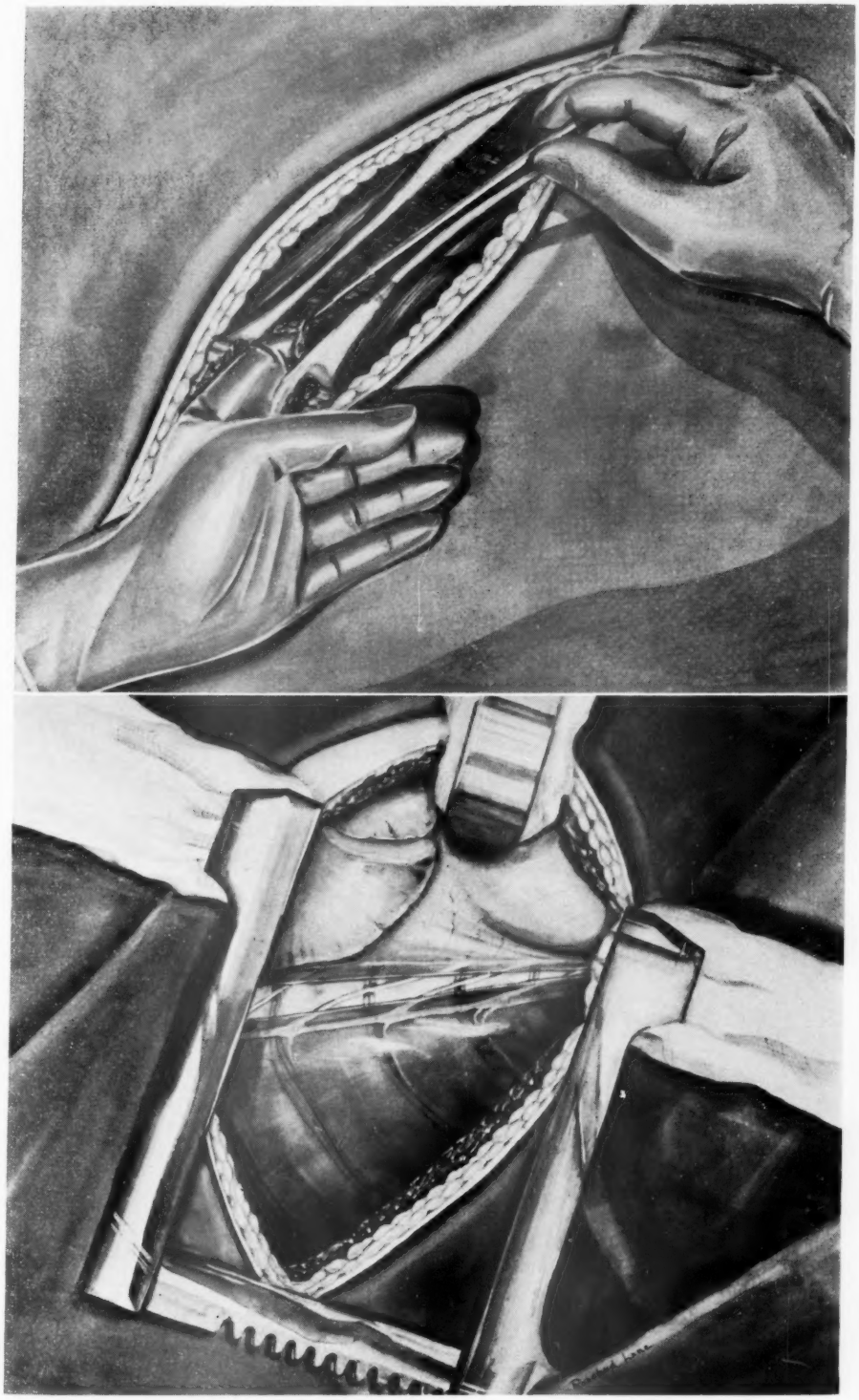


Fig. 3.

Fig. 2.—The incision of the intercostal muscles and the parietal pleura is placed exactly midway between the two ribs.

Fig. 3.—The chest has been opened, the ribs separated, and the vertebral pleura has been incised midway between the great splanchnic nerve and the sympathetic chain.

Fig. 4.

Fig. 5.

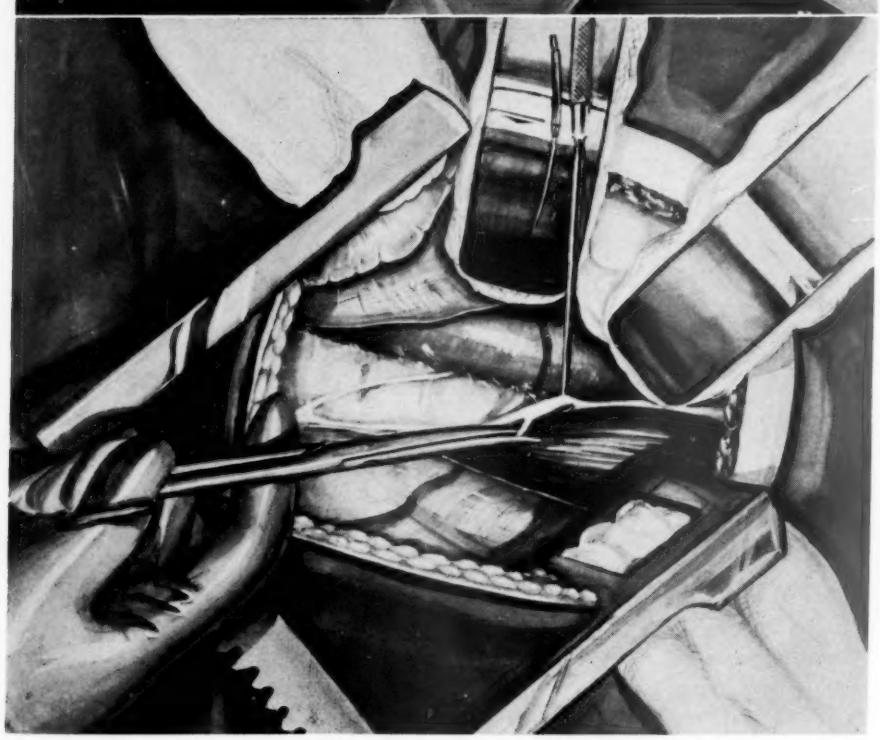
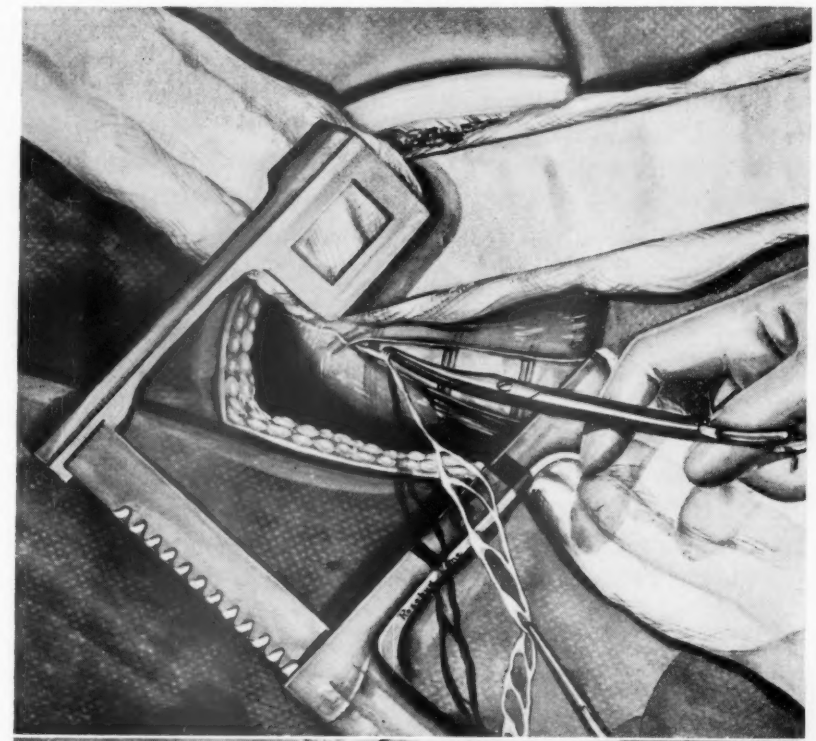


Fig. 4.—The incision in the diaphragm is made parallel to and 3 cm. from its costal attachment. The left index finger pushes the parietal peritoneum out of the way.

Fig. 5.—The medial portion of the diaphragm and the kidney are retracted. The psoas muscle has been freed of its fascial covering. The first lumbar ganglion is mobilized and its communicating branches are to be severed.

Fig. 6.



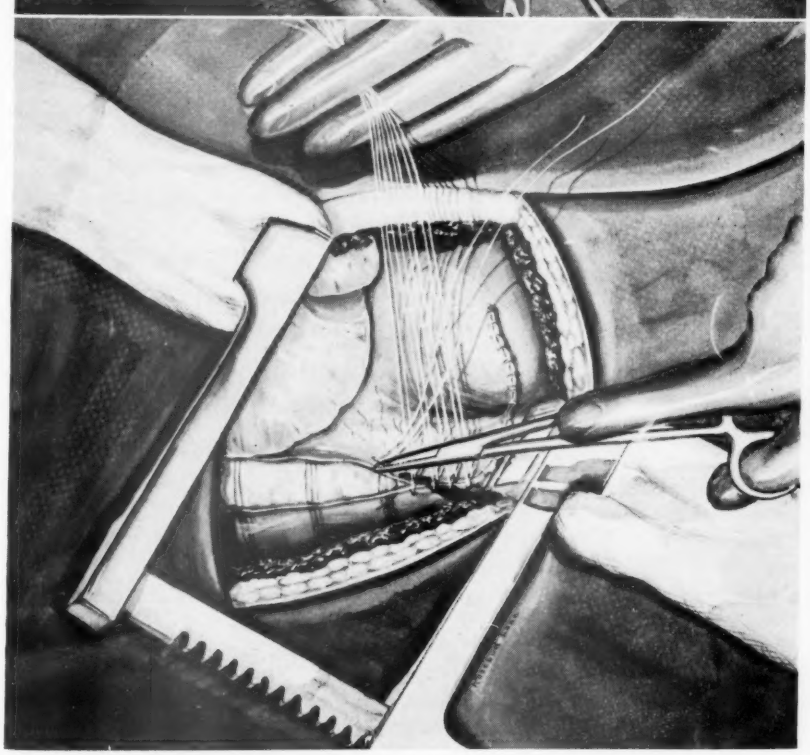


Fig. 7.

Fig. 6.—The upper thoracic portion of the sympathetic trunk is being mobilized. The chain crosses a large tributary of the azygos vein.

Fig. 7.—The incision in the diaphragm has been repaired. The lowermost portion of the opening in the vertebral pleura is being closed with interrupted cotton sutures.

ganglion depending upon the patient's preoperative condition and the response to the operation. When a patient has electrocardiographic evidence of coronary artery disease or a history of angina pectoris, an effort is made to extend the sympathectomy especially on the left to include the third and sometimes the second thoracic sympathetic ganglion. The uppermost extent of the sympathectomy is marked with a dura clip before the chain is severed.

The first step in the closure is the reconstruction of the diaphragm with interrupted No. 40 cotton sutures. The lowermost fourth of the incision in the vertebral pleura is also closed with the same material. The remaining portion of the longitudinal opening in the pleura is not sutured inasmuch as it overlies the vertebral bodies and hence is not subject to respiratory motion (Fig. 7).

The thoracotomy incision is closed in layers using interrupted No. 20 cotton for the parietal pleura and intercostal muscles, continuous fine chromicized catgut for the other muscle layers, cotton or silk for the skin. During the closure a large rubber catheter is placed in the pleural cavity in order to provide a vent through which air may escape as the lung is re-expanded under positive pressure. The catheter is removed after the closure is completed.

RESULTS

In order to evaluate this intercostal operation a comparison was made between twenty-six consecutive sympathectomies performed by this method and a like number performed by the retropleural approach after resection of the ninth or tenth rib. Ideally, such a comparison should be made by using both procedures on the same patient, the one on one side, the other on the other side. Two patients were treated in this manner. However, the convalescence in each case was so much more comfortable and rapid after the intercostal approach that we no longer felt justified in using any other procedure. Consequently, the next twenty-four intercostal operations were compared with a like number previously performed with rib resection.

The extent of the sympathectomy achieved by each of the two procedures is shown in Table I. By the retropleural approach we were able to excise the sympathetic chain above the level of the third thoracic ganglion only once. When the intercostal approach was used, the exposure of the upper thoracic

TABLE I. EXTENT OF THORACOLUMBAR SYMPATHECTOMY

LEVEL OF EXCISION	AFTER RIB RESECTION	AFTER INTERCOSTAL APPROACH
Upper		
D2	0	3
D3	1	5
D4	5	9
D5	9	6
D6	11	1
D7	0	1
D8	0	1
Lower		
L1	1	0
L2	22	23
L3	3	2
L4	0	1

chain was improved so that it was possible to remove the third dorsal ganglion in five cases and the second dorsal ganglion in three cases. On one occasion the operation was discontinued at the eighth thoracic level because of cardiac arrest and in another patient the sympathectomy was stopped above the seventh dorsal ganglion because of an alarming drop in the patient's blood pressure. Both these patients were operated upon by the intercostal approach. More extensive sympathectomies could easily have been performed in each instance.

The exposure of the lumbar sympathetic chain is about the same in the two approaches. Little difficulty was encountered in excising the first two lumbar ganglia. In one case the sympathectomy was extended down to include the fourth ganglion. This more extensive removal was possible because of the earlier removal of a large hydronephrotic kidney at the same operation and could not be credited to better exposure resulting from the use of the intercostal operation.

A comparison of the upper limits of sympathectomy achieved by the two types of approach is presented in graphic form in Fig. 8. The complications incident to each operative procedure are shown in Table II and in Fig. 9.

TABLE II. POSTOPERATIVE COMPLICATIONS FOLLOW THORACOLUMBAR SYMPATHECTOMY

COMPLICATION	AFTER RIB RESECTION	AFTER INTERCOSTAL APPROACH
Pneumothorax	5	1
Pleural effusion	14	0
Empyema	2	0
Pneumonitis	3	1
Atelectasis	1	1
Wound separation	1	2
Intercostal neuralgia	6	3
Deaths	1	0

Whereas five patients required aspiration of a residual pneumothorax following the retropleural operation, this complication was encountered only once after our transpleural operation. The difference in the incidence of serious pleural effusion is even more striking: over 50 per cent after the retropleural approach, none after the transpleural approach. Inasmuch as the two cases of empyema resulted from infection of sanguineous pleural effusions, this complication was not encountered in the group subjected to the intercostal operation. The incidence of postoperative neuralgia was significantly higher after rib resection than in those patients who had an intercostal incision. The one operative death in the series followed the retropleural operation. Death occurred on the twenty-fourth postoperative day due to congestive heart failure. A large pleural effusion and a pneumonitis contributed significantly to the fatal outcome.

The only postoperative complication encountered more frequently after the intercostal procedure was wound separation. The figures for the two series are too small to be statistically significant, but a higher incidence of dehiscence would not be unexpected since the closure of the intercostal incision is somewhat more difficult.

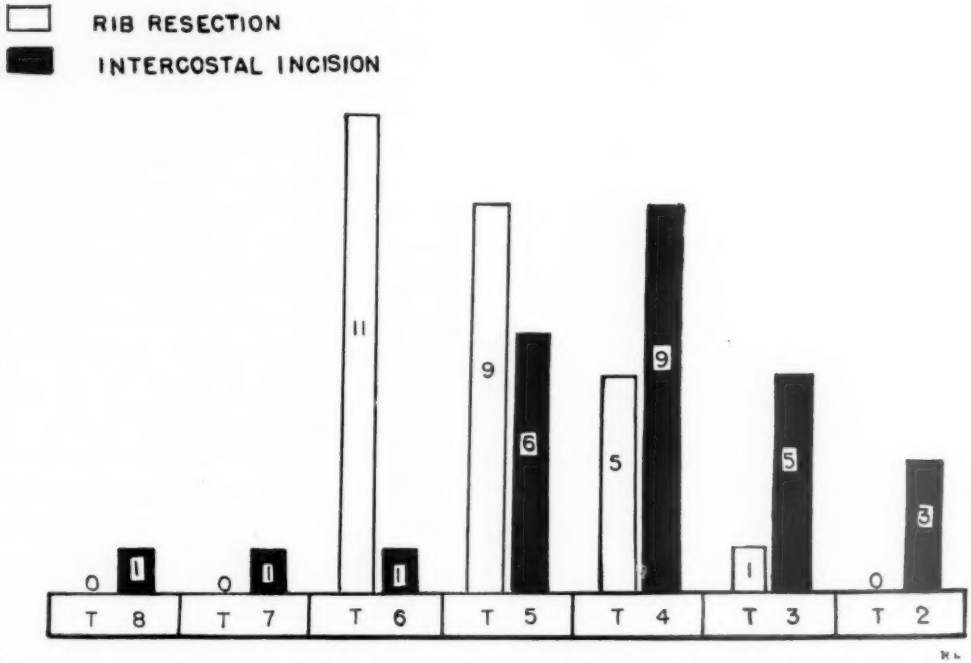


Fig. 8.—A comparison of the upper limit of sympathectomy attained by a retropleural approach with resection of the ninth or tenth rib and that attained by an intercostal, transpleural approach. Twenty-six operations were performed by each technique. It is apparent that the upper thoracic sympathetic chain is more accessible in the intercostal operation.

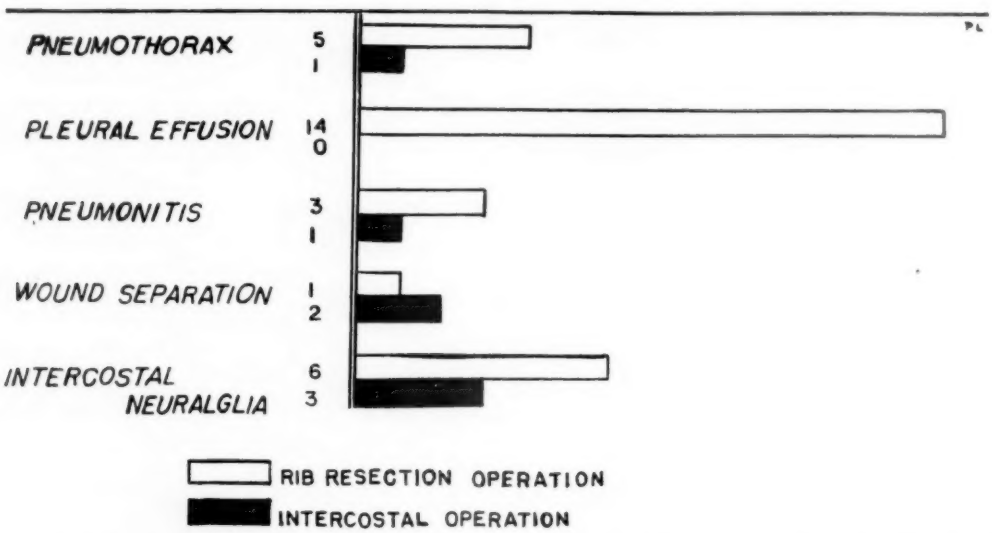


Fig. 9.—A comparison of the incidence of postoperative complications in twenty-six thoracolumbar sympathectomies by a retropleural approach with rib resection and a like number performed by an intercostal transpleural approach. The latter procedure is followed by fewer complications than are encountered after the former.

DISCUSSION

There is little doubt that an intercostal transpleural approach to the thoracolumbar sympathetic chain provides better exposure and causes less trauma than the commonly used retropleural approach with rib resection. Because of the better exposure, the lighting of the operative field is easier and there is less danger of injuring an intercostal vessel. The more extensive removal of the thoracic sympathetic chain which is made feasible by better exposure is desirable in order properly to achieve the therapeutic objective of the operation.[9] While Hinton and Lord[14] advocate a return to the classical Smithwick procedure in patients of the older age group, they nevertheless observed a more satisfactory drop in blood pressure following Hinton's more extensive operation. Apparently the dissatisfaction with a more radical sympathectomy arose largely from the higher mortality and morbidity encountered in older patients. Inasmuch as the intercostal operation is fraught with much less danger, there is no advantage in utilizing a therapeutically less effective procedure. Furthermore, it seems advantageous to extend the upper limit of sympathetic denervation in patients with coronary artery disease. Three patients in our series with a history of severe angina pectoris reported marked amelioration of anginal pain following left sympathectomies which included the second or third thoracic ganglion.

An additional technical advantage of the transpleural approach was encountered in two patients who had peptic ulcer as well as hypertension. In both cases a vagotomy was performed along with the left sympathectomy. The exposure and section of the vagus nerves added little to the duration or trauma of the operation.

The reduction in the incidence of complications after the intercostal operation seemed to confirm the hypotheses by which we had sought the explanation of their origin. Thus, there were no serious pleural effusions, no cases of postoperative empyema, and only one residual pneumothorax, when we ceased to separate large areas of parietal pleura from the chest wall. Even the reduction in incidence of pneumonitis seemed to have a plausible basis in a more comfortable postoperative course with relatively unrestricted respiratory movements. However, there were still cases of intercostal neuralgia, previously attributed to rib resection. It is not unlikely that at times the intercostal nerve might have been traumatized by rapid expansion of the Finochietto rib spreader or even included in the sutures used for the innermost layer of the thoracotomy closure.

In our experience the only contraindication to the intercostal transpleural operation is obliteration of the pleural cavity by a healed pleuritis. However, the presence of a moderate number of adhesive bands between the lung and parietal pleura in two cases merely resulted in a slight prolongation of the operation without significantly affecting the postoperative course.

It is well recognized that certain postoperative complications such as coronary thrombosis and peripheral vascular accidents are to be anticipated after extensive sympathectomy by any method. Attempts at prevention have

included the judicious use of sympathicomimetic drugs, the intravenous infusion of blood and other fluids during and after operation, a regime of voluntary deep breathing, leg exercises, and early ambulation. The greater comfort experienced by our patients after intercostal sympathectomy has facilitated the maintenance of this regime.

SUMMARY

In the evolution of the surgical treatment of arterial hypertension the trend has been toward increasingly more extensive sympathetic denervation. The procedures by which this has been achieved have often been associated with inherent technical difficulties to which have been attributed a high incidence of postoperative complications. An operative technique is described by which an extensive thoracolumbar sympathectomy is performed by a transpleural approach without rib resection. Following this procedure there is a marked decrease in the frequency of the complications ordinarily encountered after a retropleural operation with rib resection.

REFERENCES

1. Bruning, F.: Die operative Behandlung der Angina Pectoris durch Exstirpation des Halsbrustsympathicus und Bemerkungen über die operative Behandlung der abnormen Blutdrucksteigerung, Klin. Wchnschr. **2**: 777, 1923.
2. Adson, A. W., and Brown, G. E.: Malignant Hypertension. Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots From the Sixth Thoracic to the Second Lumbar, Inclusive, J. A. M. A. **102**: 1115, 1934.
3. Craig, W. McK.: Surgical Approach to and Resection of the Splanchnic Nerves for Relief of Hypertension and Abdominal Pain, West. J. Surg. **42**: 146, 1934.
4. Peet, M. M.: Splanchnic Section for Hypertension: A Preliminary Report. Univ. Hosp. Bull., Ann Arbor **1**: 17, 1935.
5. Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension, SURGERY **7**: 1, 1940.
6. Grimson, K.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in Treatment of Hypertension, Ann. Surg. **114**: 753-755, 1941.
7. Hinton, J. W., and Lord, J. W., Jr.: Operative Technique for Thoracolumbar Sympathectomy, Surg., Gynec. & Obst. **83**: 643, 1946.
8. Poppen, J. L., and Lemmon, C.: Surgical Treatment of Hypertension, J. A. M. A. **134**: 1, 1947.
9. Goetz, R. H.: The Surgical Physiology of the Sympathetic Nervous System With Special Reference to Cardiovascular Disorders, Internat. Abstr. Surg. **87**: 417, 1948.
10. Linton, R. R., Moore, F. D., Simeone, F. A., Welch, C. E., and White, J. C.: Thoracolumbar Sympathectomy for Hypertension, S. Clin. North America **27**: 1178, 1947.
11. Linton, R. R.: Personal communication.
12. Weinberg, J. A., and Kraus, A. R.: Intercostal Incision in Transpleural Operations, J. Thoracic Surg. (To be published.)
13. Weinberg, J. A.: Personal communication.
14. Hinton, J. W., and Lord, J. W., Jr.: The Surgical Treatment of Essential Hypertension, S. Clin. North America **28**: 290, 1948.

SEBACEOUS GLANDS AND SEBACEOUS GLAND-CONTAINING TUMORS OF THE PAROTID SALIVARY GLAND

With a Consideration of the Histogenesis of Papillary Cystadenoma Lymphomatosum

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TUMORS of the salivary glands have been the subject of a great deal of study, and the remarkable variations which their histologic pictures may present are familiar features. Within the past one and one-half years, we encountered two tumors of the parotid salivary gland which differed strikingly from all of the other 160 salivary gland tumors studied in the Laboratory of Surgical Pathology of the Hospital of the University of Pennsylvania. One of these tumors was characterized by the inclusion of structures indistinguishable from sebaceous glands, the other by groups of cells identical with those of sebaceous glands. No reports of similar tumors have been found in an extensive search of the literature.

Subsequently, in the salivary gland tissue resected with a recurrent cylindromatous tumor of the parotid gland, normal-appearing sebaceous glands were observed to arise from the ducts of several of the gland lobules not involved by the tumor. Similar findings have been described by Hartz,[1] Lee,[2] and Meza-Chávez.[3] Hartz observed a few sebaceous glands in the normal salivary gland tissue attached to the periphery of an excised mixed tumor of the parotid. Lee described a case in which a mass in front of the left ear was removed. It proved to be a hyperplastic lymph node, but in a fragment of adjacent parotid salivary gland diffusely scattered sebaceous glands were observed. Meza-Chávez observed sebaceous glands associated with the ducts of two parotid glands resected for adenomas.

The sebaceous gland-bearing tumors we have encountered bear certain resemblances, especially striking in one of the cases, to the salivary gland papillary cystadenoma lymphomatosum, and their study has appeared to shed some light on the question of the histogenesis of this tumor type.

The following reports include one case in which normal-appearing sebaceous glands were found within the parotid substance, the fifth instance known to us, and two cases of tumorous masses of the parotid composed in part of sebaceous gland elements. These two tumors are, so far as we are aware, the first of their kind to be described.

CASE REPORTS

Case 1.—D. Z., a 34-year-old white man, was admitted to the Hospital of the University of Pennsylvania in February, 1948, with a tumor of the right parotid salivary gland of five years' duration. This was excised but promptly recurred and secondary surgical procedures for recurrent tumors were performed in November, 1948, and in January, 1949. The histologic appearance in each instance was that of a cylindroma.

The pathologic specimen removed at the third operation included much uninvolved parotid tissue in addition to the tumor. As an incidental finding, typical sebaceous glands

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were noted within the otherwise normal salivary gland tissue (Fig. 1). Serial sections showed that the sebaceous glands, although numerous, were limited to only a few lobules. The majority of lobules contained none of these structures. The sebaceous glands could be seen to arise from intralobular parotid ducts, both striated and intercalated as previously noted by Hartz.[1]

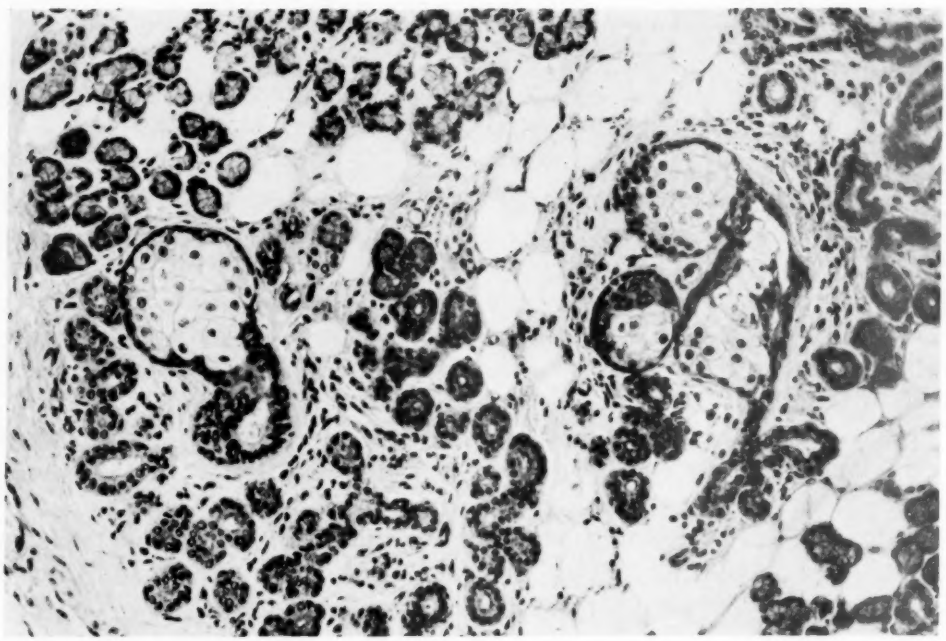


Fig. 1 (Case 1).—Within a single lobule of normal parotid gland tissue are two groups of sebaceous glands. The sebaceous gland on the right is seen to arise from a striated intralobular duct. (Hematoxylin and eosin, ×180.)

CASE 2.—S. S., a 66-year-old white woman, was admitted to the Medical Service of the Hospital of the University of Pennsylvania in April, 1948, in cardiac failure. She was found to have severe arteriosclerotic cardiovascular disease and diabetes mellitus. An incidental finding on examination was a mass in the left parotid region. This was excised; at operation it was found to lie within the parotid salivary gland. The patient died three weeks later at home, presumably as the result of cardiovascular disease.

Pathologic Description.—The lesion consisted of a firm, solid, well-encapsulated mass of white tissue measuring 3.2 by 2.8 by 2.0 cm. The microscopic pattern was complex and striking. Resting on a fairly dense lymphoid stroma, showing follicular organization with germinal centers, were numerous dilated ductlike spaces. These were lined by a single layer of tall columnar cells having eosinophilic granular cytoplasm and small, uniform, round, somewhat vesicular nuclei which seemed to lie at two different levels with relation to the basal poles of the cells. There was scanty secretion within the lumina which contained both mucin and lipoid material. Arising from the walls of many of these structures were well differentiated sebaceous glands which for the most part lay beneath the eosinophilic columnar layer and in many places extended out into the lymphoid stroma (Fig. 2). The cells of the sebaceous glands were large, with large, round central nuclei, and their cytoplasm was composed of large, closely packed vacuoles. Fat stains showed that the vacuoles represented lipoid droplets (Fig. 3). Mucicarmine stains revealed no mucin within the sebaceous glands although mucicarminophilic material was present within the ductlike structures. Mitoses were not in evidence and no invasion of normal tissue or capsule was seen. We have regarded this tumor as benign.

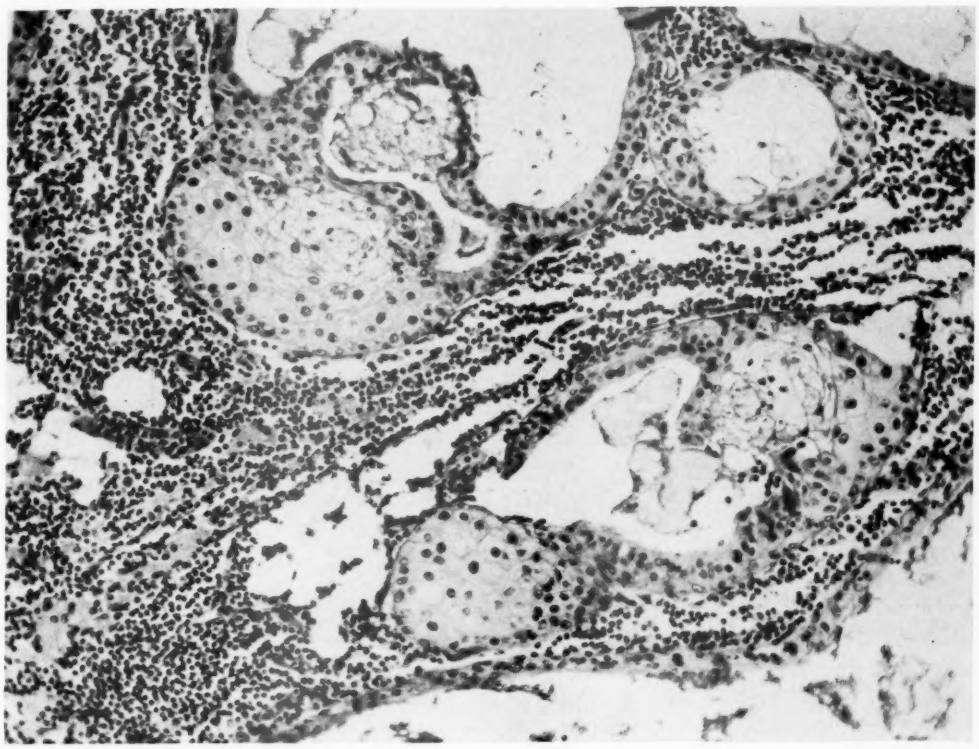


Fig. 2 (Case 2).—The tumor consists of ductlike structures resembling those of the papillary cystadenoma lymphomatosum, which are set in a lymphoid stroma. Arising from these ducts are numerous well-formed sebaceous glands. (Hematoxylin and eosin, ×185.)

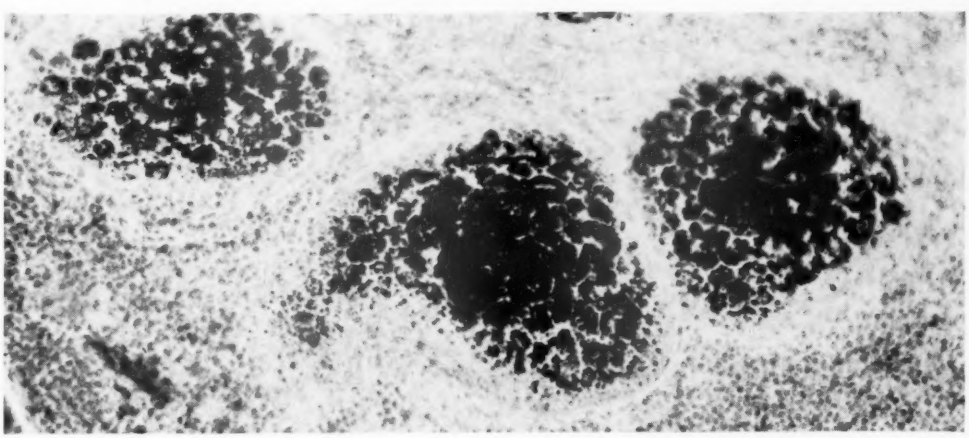
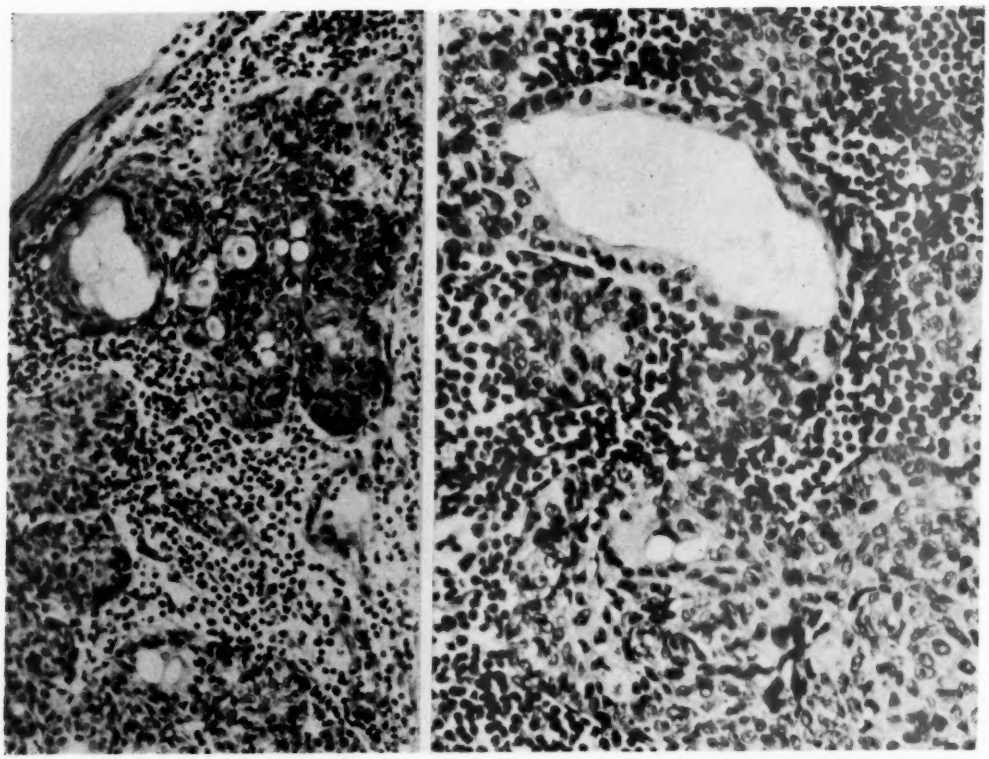


Fig. 3 (Case 2).—The dark-staining areas represent fat globules within the sebaceous glands of the tumor. (Sudan IV, ×200.)

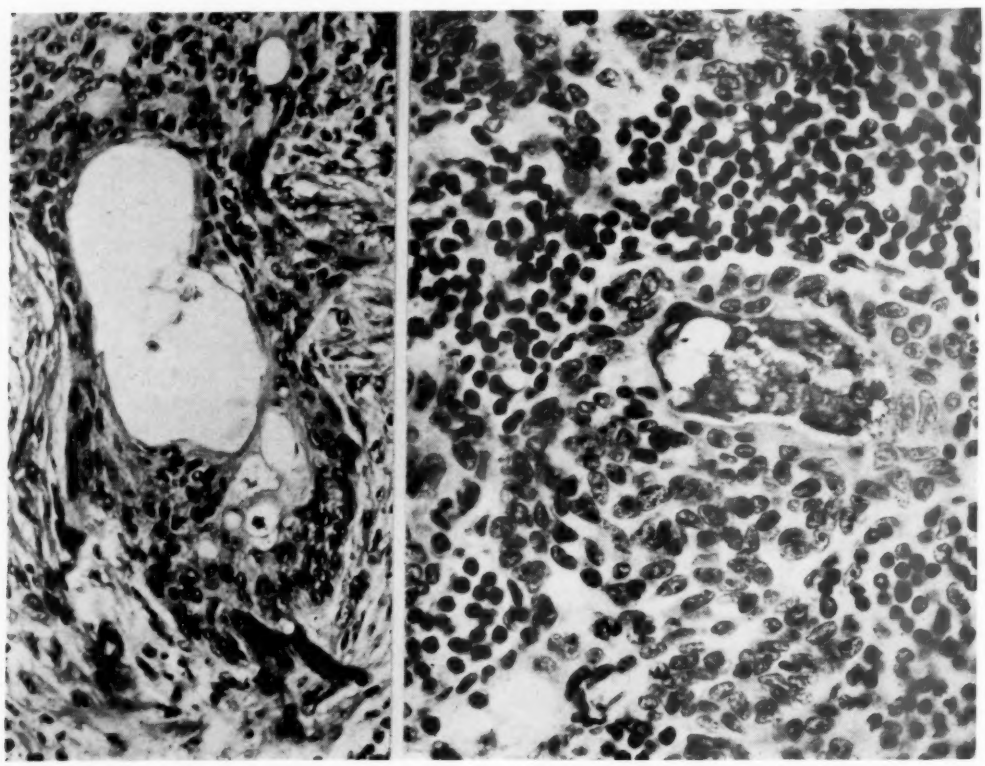
Case 3.—J. K., a 69-year-old white woman, had noted a painless swelling in front of the left ear for eight months. This was the size of a pea when first noted and grew slowly. She was admitted to the Surgical Service of the Hospital of the University of Pennsylvania in February, 1948. The tumor was easily shelled out from its bed in the parotid gland and the patient was well and free of recurrence when seen four months later.

Pathologic Description.—The lesion consisted of a slightly lobulated, ovoid, firm, encapsulated lesion measuring 2.0 by 1.8 by 1.2 cm. The cut surface was uniformly yellowish



A. *B.*

Fig. 4 (Case 3).—*A*, The tumor is composed of masses of epithelial cells lying in a lymphoid stroma. Cells of the sebaceous gland type are seen within the epithelial masses. (Hematoxylin and eosin, ×200.) *B*, A large ductlike structure lined by columnar cells. (Hematoxylin and eosin, ×320.)



A. *B.*

Fig. 5 (Case 3).—A, Cells of the sebaceous gland type lying adjacent to a ductlike structure in the tumor. (Hematoxylin and eosin, ×320.) *B*, The dark material within a ductlike structure of the tumor has the staining properties of mucin. (Mucicarmine stain, ×500.)

white and slightly granular. Microscopic examination revealed masses of epithelial cells lying within a dense lymphoid stroma. Many of these cell masses were solid, the cells having medium-sized, oval, slightly vesicular nuclei and relatively scant eosinophilic cytoplasm. Cell shape was variable, but many cells showed a tendency toward a spindle form. In many areas, an epidermoid character was suggested, although specific and distinct epidermoid features were lacking. In other cell cords, however, there were small groups of vacuolated cells identical with those of sebaceous glands. These cells had large, round central nuclei and close-packed, large cytoplasmic vacuoles (Fig. 4, *A*). Still other cell groups included ductlike structures lined by a single layer of fairly regular eosinophilic columnar cells having uniform, small, rounded nuclei which were situated at two different levels within the cells (Fig. 4, *B*). Some of these ductlike structures included vacuolated cells of sebaceous gland within their walls (Fig. 5, *A*). Mitoses were not observed. No invasion of surrounding tissue was seen. Mucicarmine stain of the tumor showed mucin to be present in the ductlike structures, but not in the cells of sebaceous gland type (Fig. 5, *B*). This tumor, too, we have been inclined to regard as benign, although its benign nature is not so clear as in Case 2. If, on the basis of mucin secretion and the suggestive epidermoid character, we classify it with the muco-epidermoid tumors[4] then we might expect it to behave as a tumor of a low grade of malignancy.

DISCUSSION

Embryologists agree that the parotid gland, along with the other major salivary glands, is of ectodermal origin, arising from the wall of the embryonic oral cavity through the growth of a solid epithelial bud into the underlying mesenchyme.[5-8] The original epithelial bud ramifies into a treelike structure in which a lumen gradually appears. When the lumen reaches the terminal bud the latter ceases to grow and specific differentiation with development of zymogen granules and mucin secretion takes place. Since, then, the parotid salivary gland is to be regarded as of ectodermal origin, the fact that its ducts may occasionally develop accessory structures similar to those of the epiderm may reasonably be accounted for. Hartz[1] has shown by means of serial sections that the sebaceous glands in his case arose as branching outgrowths of the parotid ducts, either striated or intercalated. This finding was confirmed in our Case 1. According to Weatherford,[9] sebaceous glands develop in the mucosa of the cheek at puberty, and Margolies and Weidman[10] found them in this situation along the interdental line or in the mucous membranes of the lips in 70 per cent of adults. This area of the buccal mucosa corresponds with the site of origin of the parotid gland in embryonic life.

Papillary Cystadenoma Lymphomatosum.—Despite differing considerably in appearance, the tumors reported have certain features in common with each other as well as with the papillary cystadenoma lymphomatosum. Both have an essential structure of epithelial elements set in a dense lymphoid stroma which does not have the sinusoidal architecture of a lymph node. In Case 2 the epithelial elements consist of dilated ductlike structures closely resembling those of the papillary cystadenoma lymphomatosum. Indeed, the general appearance of this tumor suggests a papillary cystadenoma lymphomatosum, some of the ducts or cysts of which have given rise to sebaceous glands. The tumor in Case 3 is less well organized and presents a more variable picture. Although mucin secretion and a tendency toward epidermoid differentiation bring to mind the

muco-epidermoid tumor, nevertheless, the appearance of some of the ductlike structures, together with the relationship of the epithelial elements to the lymphoid stroma, suggests again the papillary cystadenoma lymphomatosum.

This apparent relationship is too striking to ignore, and it seems relevant to inquire into the histogenesis of the papillary cystadenoma lymphomatosum. The material of the Laboratory of Surgical Pathology of the Hospital of the University of Pennsylvania includes six tumors in this category. Their clinical and pathologic features have been recorded elsewhere,[11] but each has been restudied in connection with the tumors reported here with special regard to the problem of their histogenesis.

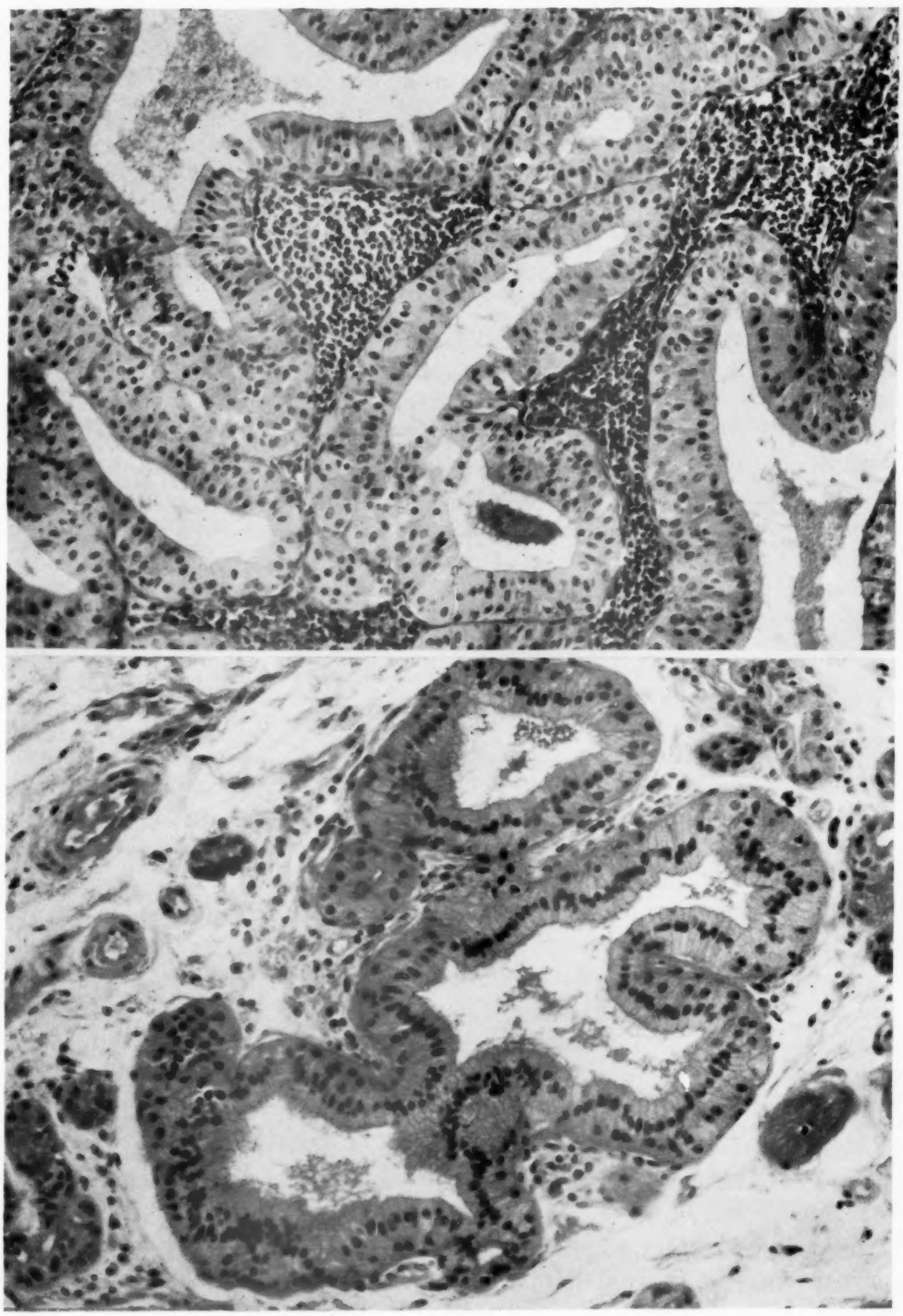
The histologic features of these cases of papillary cystadenoma lymphomatosum support, in our opinion, the concept of origin from salivary ducts. Unless there are strong reasons for believing otherwise, it is reasonable to assume that a given benign tumor has arisen from normal components of the tissue in which it is found rather than from a cell rest whose occurrence is unproved. The principal point favoring origin from salivary ducts is the resemblance of the ductlike structures of the papillary cystadenoma lymphomatosum to the interlobar ducts of the salivary glands of many older individuals (Fig. 6). Both are lined by tall columnar cells with granular, eosinophilic cytoplasm with variable numbers of mucin-secreting goblet cells interspersed. The morphologic resemblance is even more striking when these tumors are compared with certain instances of chronic inflammatory disease of the salivary glands. The fact that three instances of papillary cystadenoma lymphomatosum have been reported in the submaxillary salivary gland,[12, 13, 14] even though the vast majority occur in the parotid, further supports origin from normal salivary gland structures as opposed to origin from vestigial remnants.

The architecture of the tumor in Case 2 may well be accounted for by postulating that the included sebaceous glands arose from the ductlike structures of a papillary cystadenoma lymphomatosum just as they arose from normal salivary ducts in Case 1 and in the cases reported by Lee, Hartz, and Meza-Chávez. The same explanation might be applied to the tumor in Case 3 but it is also possible that in this case the sebaceous gland cells complicate a tumor fundamentally of some other type, perhaps muco-epidermoid. Thus, it seems reasonable to presume that the tumors themselves are of salivary duct origin.

The opinion held by some[15] that the papillary cystadenoma lymphomatosum arises from oncocytes is entirely compatible with the idea of salivary duct origin. Oncocytes are described as large cells with abundant eosinophilic granular cytoplasm which are not infrequently found in the salivary ducts and acini of older individuals.[3] These cells closely resemble those of the papillary cystadenoma lymphomatosum (Fig. 6). The fact that these tumors characteristically occur in older individuals is in harmony with this view.

The close association of lymphocytes with the epithelial elements of the tumor has long been a great stumbling block. However, Bauer[16] pointed out that epithelial areas are frequently seen devoid of lymphoid stroma. This is also true in the material we have studied. On this basis, Bauer suggested that the epithelial areas proliferate independently, and that lymphoid stroma is

A.



B.

Fig. 6.—*A*, Papillary cystadenoma lymphomatosum. Note tall columnar cells with nuclei which tend to lie at two distinct levels. (Hematoxylin and eosin, ×200.) *B*, Oncocytes lining an interlobar duct of a salivary gland. Note tall columnar cells with nuclei which tend to lie at two distinct levels. (Hematoxylin and eosin, ×200.)

formed only secondarily. This type of relationship between lymphoid and epithelial tissues is not peculiar to the papillary cystadenoma lymphomatosum. It is also found, for example, in many testicular tumors, the ovarian dysgerminoma, and the lymphoepithelioma of the nasopharynx. Neisse[17] and others[13, 18, 19] have attempted to explain the lymphoid stroma by postulating the origin of the tumor from heterotopic salivary gland tissue in lymph nodes. Although these writers have observed such heterotopic tissue, it has never been demonstrated to be the site of origin of a tumor. Furthermore, the lymphoid stroma of the tumor does not have the sinusoidal structure of a lymph node, but rather consists of masses of lymphoid cells, often containing germinal centers.

Most of the other theories of origin of the papillary cystadenoma lymphomatosum are based upon derivation from cell rests. These embryonic structures include: (1) a branchiogenic arch,[20-23] (2) heteroptopic pharyngeal ectoderm,[12, 24] (3) the orbital inclusion,[25] and (4) misplaced thymic anlage.[26] Origin of the tumor from lymph vessel endothelium by a process of metaplasia has also been suggested.[26] In view of the sound reasons for believing the papillary cystadenoma lymphomatosum to arise from salivary ducts, it seems unnecessary to invoke these various devious mechanisms. For discussions of these many theories the reader is referred to the articles of Plaut[27] and of Martin and Ehrlich.[28]

Before we observed normal-appearing sebaceous glands within salivary gland tissue or became aware of the similar observations of others, we had also considered the possibility of a relationship of these two tumors (especially Case No. 3) to the muco-epidermoid tumors. There are certain definite resemblances, chiefly the occurrence in the lesions of epithelial cells of a variety of forms and types. In both our tumors the variety included mucus-secreting cells, columnar cells, and undifferentiated basal cells, and Case 3 included also many cells of an epidermoid appearance. It is of interest that Stewart, Foote, and Becker[4] have postulated an origin from the largest intermediate salivary ducts for the muco-epidermoid tumors.

A wide variety of types of epithelial cell characterize the ducts of the normal (and chronically inflamed) salivary glands,[4, 5, 29] and the equally great variety of tumor types whose origin has been assigned to these ducts need occasion no surprise.

SUMMARY

A case is reported in which sebaceous glands were found to arise from ducts of the parotid salivary gland. Four similar cases have previously been reported in the literature.

Two tumors of the parotid gland containing sebaceous gland elements are reported. One of these closely resembled the papillary cystadenoma lymphomatosum with, however, the addition of well-formed sebaceous glands. The other tumor, having a less striking resemblance to the papillary cystadenoma lymphomatosum and simulating in some degree the muco-epidermoid tumor, contained, usually in small clusters, cells identical with those characterizing normal sebaceous glands.

The probable origin of the papillary cystadenoma from salivary gland ducts is discussed.

REFERENCES

1. Hartz, P. H.: Development of Sebaceous Glands From Intralobular Ducts of the Parotid Gland, Arch. Path. **41**: 651, 1946.
2. Lee, C. M., Jr.: Intraparotid Sebaceous Glands, Ann. Surg. **129**: 152, 1949.
3. Meza-Chávez, L.: Oxyphilic Granular Cell Adenoma of the Parotid Gland (Oncocytoma), Am. J. Path. **25**: 523, 1949.
4. Stewart, F. W., Foote, F. W., and Becker, W. F.: Mucoepidermoid Tumors of Salivary Glands, Ann. Surg. **122**: 820, 1945.
5. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, 1944, W. B. Saunders Company.
6. Patten, B. M.: Human Embryology, Philadelphia, 1947, The Blakiston Company.
7. Arey, L. B.: Developmental Anatomy, Philadelphia, 1936, W. B. Saunders Company.
8. Dodds, G. S.: Essentials of Human Embryology, London, 1935, John Wiley & Sons, Inc.
9. Weatherford, H. L.: A Textbook of Histology, Philadelphia, 1944, The Blakiston Company, p. 319.
10. Margolies, A., and Weidman, F.: Statistical and Histologic Studies of Fordyce's Disease, Arch. Dermat. & Syph. **3**: 723, 1921.
11. Rawson, A. J., and Howard, J.: Salivary Gland Tumors; Clinico-pathologic Study. (To be published.)
12. Wendel, A., Jr.: Papillary Cystadenoma Lymphomatosum; Case Report; Rare Teratoid of Submaxillary Gland, J. Cancer Research **14**: 123, 1930.
13. Albrecht, H., and Arzt, L.: Beiträge zur Frage der Gewebsverirrung. 1. Papilläre Cystadenome in Lymphdrüsen, Frankfurt. Ztschr. f. Path. **4**: 47, 1910.
14. Spitznagel: Vereinigung pathologische Anatomie Wiens., Wien. klin. Wchnschr. **42**: 983, 1929.
15. Jaffe, R. H.: Adenolymphoma (Onkocytoma) of Parotid Gland, Am. J. Cancer **16**: 1415, 1932.
16. Bauer, W. H.: in Anderson, W. A. D.: Pathology, St. Louis, 1948, The C. V. Mosby Company.
17. Neisse, R.: Ueber den Einschluss von Parotisläppchen in Lymph knoten, Anat. Hefte **10**: 289, 1898.
18. Nicholson, G. W.: Studies on Tumor Formation; Tissue Malformations; Anomalies of Position and of Blending, Guy's Hosp. Rep. **72**: 333, 1922.
19. Bunting, H., and Tennant, R.: Personal communication; quoted by Plaut.[27]
20. Ssobolew, L. W.: Zur Kasuistik der Branchiome, Frankfurt. Ztschr. f. Path. **11**: 462, 1912.
21. Askanazy, In Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Vol. 1, part 1, Berlin, 1926, Julius Springer, p. 333.
22. Rikl, A.: Kasuistischer Beitrag zu der Frage der Parotistumoren, Centralbl. f. allg. Path. u. path. Anat. **35**: 310, 1924.
23. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1914, W. B. Saunders Company, p. 798.
24. Warthin, A. S.: Papillary Cystadenoma Lymphomatosum; Rare Teratoid of Parotid Region, J. Cancer Research **13**: 116, 1929.
25. Kraissl, C. J., and Stout, A. P.: "Orbital Inclusion" Cysts and Cysto-Adenomas of Parotid Salivary Glands, Arch. Surg. **24**: 485, 1933.
26. Robinson, D. W., and Harless, M. S.: Papiliary Cystadenoma Lymphomatosum of the Parotid Gland, Surg., Gynec. & Obst. **76**: 449, 1943.
27. Plaut, J. A.: Adenolymphoma of the Parotid Gland, Ann. Surg. **116**: 43, 1942.
28. Martin, H., and Ehrlich, H. E.: Papillary Cystadenoma Lymphomatosum (Warthin's Tumor) of the Parotid Salivary Gland, Surg., Gynec. & Obst. **79**: 611, 1944.
29. Sheldon, W. H.: So-called Mixed Tumors of the Salivary Glands, Arch. Path. **35**: 1, 1943.

FUNCTIONAL RECOVERY FOLLOWING THE USE OF HOMOGENOUS NERVE GRAFTS

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A STUDY was made upon the recovery of function following the use of homogenous nerve grafts in cats and in man. Unions were accomplished with the plasma clot and silk suture techniques and comparisons between the two methods were made.

The following objections have been made to the conventional suture technique: (1) It is difficult to avoid inclusion of nerve fibers in the suture; (2) there may be "knuckling" of the nerve fascicles when the epineurium is sutured to epineurium; (3) all suture materials are foreign to the body and cause tissue reactions which result in fibrosis.[1]

Young and Medawar[2] were the first to approximate divided nerve ends without using sutures. In 1940, they united nerve ends with fortified cockerel plasma coagulated by chick embryo extract. They held the divided ends together with jeweler's forceps until coagulation was complete. In 1942, Tarlov and Benjamin,[3] following the suggestion of Young and Medawar, used cockerel plasma with chick embryo extract as a clotting agent and found considerable inflammatory reaction with fibrosis at the site of nerve union. This stimulated them to try unmodified autologous plasma. Since then there have been gradual improvements in the technique. Shapiro and Tarlov[4] have used different types of preserved plasmas—sodium citrate plasma, potassium oxalate plasma, and dried plasma, but because of their dilution, all were found to have a low tensile strength. Use of unmodified plasma was difficult in that it entailed the use of syringes coated with mineral oil and paraffin-lined test tubes packed in ice to prevent coagulation until the nerves were to be approximated. They found heparin to be an excellent anticoagulant because a minute quantity kept the plasma liquid. Protamine sulfate could be used to neutralize the anticoagulating effect of heparin and permit the plasma to clot when it was added to the heparinized plasma. Tarlov[5] also devised latex molds within which the divided nerve ends could be placed end to end and held until the plasma formed a clot sufficiently strong to keep the ends in approximation.

The plasma method of union of nerve ends with and without the use of latex molds has been used by different workers both experimentally and clinically. There has been agreement that it is workable except where there is tension.[2, 5] Therefore, it has frequently been incorporated with the use of silk or tantalum sutures which are used to aid in overcoming the tension.[6]

In this study, it was desired to establish a condition in which the plasma clot technique could be used without the aid of sutures. Since all divided nerves that are re-approximated have varying degrees of tension, a simple end-to-end union could not be performed. Merely sectioning the sciatic nerve of a cat causes the divided ends to retract so that when they are reapproximated there is some tension. Therefore, the use of a graft was employed because this could

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be of sufficient length to overcome easily any gap between the divided ends occurring when the nerve was severed.

Previous work had been done by Davis, Perret, Hiller, and Carroll,[7] in which nerve grafts had been sutured with fine silk. Many of the animals and statistics derived from their study were used for controls, and offered excellent material for a comparative study. Sixteen of their animals were used for control studies. Eight additional cats were operated upon with the silk suture technique, making a total of twenty-four animals in the control group.

OPERATIVE PROCEDURES

The experiments were performed upon thirty-five cats and the sciatic nerve was used in all instances. Following induction by intravenous nembutal anesthesia, the operative procedures followed sterile surgical technique. The nerve was sectioned in its middle third with a new razor blade and repair was performed with the use of a 2.5 cm. fresh homogenous graft, heparinized plasma, protamine sulfate, and the molds devised by Tarlov. No type of postoperative immobilization was used.

Twelve cubic centimeters of whole blood obtained by cardiac puncture were placed in each of several centrifuge tubes containing 0.05 c.c. of Liquaemin, which is a 1 per cent solution of the sodium salt of heparin, to keep it in solution. It was centrifuged for five minutes at 2,500 r.p.m. The plasma was removed and kept at room temperature until time for its use. The proximal and distal nerve ends and the corresponding ends of the graft were placed end to end on the wire racks which are part of the latex mold. Ten parts of heparinized plasma were then mixed with one part of protamine sulfate solution (150 mg. per cent). The latter was used to inactivate the heparin and thus permit the clot to form. This mixture was poured into the mold. After an interval of five to ten minutes when the clot was firm, the latex mold was removed, leaving the plasma clot around the nerve ends.

CLINICAL OBSERVATIONS

The cats were examined periodically for gait, stance, and active movements of the foot and toes; and for response to superficial and deep pain. The presence of ulcers and contractures was also noted.

Cats normally walk and stand only on the plantar surfaces of their toes. Only when they sit do their feet touch the ground. When the leg and foot muscles are paralyzed, the foot is dragged so that the weight is supported on the dorsum of the toes. This change in gait occurs following division of the sciatic nerve and is called "toe drop." When the normal animal stands on the plantar surface of the toes, the heel is elevated. Division of the sciatic nerve causes a paralysis of the gastrocnemius muscles resulting in a change of stance known as "heel drop."

Recovery from heel drop and toe drop are often late signs of recovery and persistence of toe drop may belie actual muscle recovery. With the disappearance of heel drop, the dorsum of the foot is often forced to bear weight and this may occur especially where there are contractures of the plantar flexors of the toes.

Heel drop began to disappear at 75 days in the cats whose grafts were united with plasma, and 72 per cent had recovered by 120 days. When the graft was placed with silk sutures, 59 per cent had recovered from heel drop at 120 days. Recovery from toe drop was more prolonged and at 180 days 60 per cent of the grafts united with plasma had recovered as compared to 43 per cent for the grafts sutured with silk.

Motion was tested by observing the response to painful stimuli such as pressure over the course of the sciatic nerve and pressure over the bones and joints. To judge accurately which muscles contributed in the motion, the knee and ankle joints were fixed at right angles to avoid the confusion from supplementary movements of the thigh or hip. Recovery of isolated motion was detected as early, or earlier, than the appearance of normal gait and stance. Movements appeared in the following order: plantar flexion of the foot, plantar flexion of the toes, dorsiflexion of the foot, fanning of the toes, and much later dorsiflexion of the toes.

In one of the cats whose graft was sutured with silk, plantar flexion of the foot appeared at sixty days following the operation. With this sole exception, isolated motion was rare at 90 days. However, at 120 days, 60 per cent of the cats whose grafts were sutured with silk had some isolated motion, while 64 per cent of the cats whose grafts were united with the plasma clot method had some isolated motion. At 180 days, all cats had some motion, regardless of the procedure used in placing the graft. At one year, the animals were capable of nearly all motions with the occasional exception of dorsiflexion of the toes which was the last to return.

The presence and degree of muscular contracture were determined by examining both the affected extremity and the normal extremity at the same time and in the same position. Certain standard positions were determined so that adequate comparisons could be made with the normal leg. In most instances the contractures were mild, so that with a little tension the muscle could be stretched to its normal length. However, a few contractures were very obvious and all attempts to overcome them were unsuccessful. No significant contractures were found in the hamstrings or in the gastrocnemius muscle group. The knee could be fully extended and flexed in practically all cases.

In examining the extensor contractures, a differentiation was made between those found in the anterior tibial muscles and those in the extensor digitorum longus. The extensor digitorum longus muscle was the most prone to become contracted and occasionally contractures of 40 to 80 degrees were noted. It became severely contracted in 12 per cent of the animals when the graft was sutured with silk as compared to 6 per cent when the graft was united with plasma. Motor recovery and response to direct electrical stimulation were observed in the contracted muscles as well as in the normal ones so this condition was probably due more to faulty posture than to improper innervation of the muscles.

Examination of the plantar and dorsiflexors of the toes was done by holding the ankle at right angles and the knee in flexion. The toes of the normal leg could easily be dorsiflexed as well as plantar flexed to 90 degrees with the foot.

Contractures were measured by any loss of the ability of the toes to be passively moved through the complete arc of 180 degrees. Plantar flexion was usually easier than dorsiflexion, but contractures in either group were so rare that no statistical comparisons could be made.

The only sensation that could be tested was pain. The animal's response to sharp pain was tested by pinprick and the response to deep pain was tested by pressure upon the toe and foot pads.

While division of the sciatic nerve caused a variation in the areas of analgesia produced in the animals; in all animals the lateral lower one-third of the leg and the entire lateral and plantar surfaces of the foot were completely analgesic. There was very little difference in the return of sensation in the different types of union employed to secure the graft. In both groups, some cats began to have a return of sensation to the lateral and plantar surfaces of the heel at 4 months and recovery was complete in all animals at 12 months. One animal had complete recovery at 6 months and the graft was united with plasma.

Compression of the toe pads in the normal cat results in prompt withdrawal of the entire lower extremity. After division of the sciatic nerve, compression of the toe pads causes no apparent attempt at withdrawal. Regardless of the type of approximation used to place the graft, the earliest response to deep pain was observed on compression of the second toe and this appeared at 120 days. Response to compression of the third toe appeared next and at 1 year all animals responded to compression of all toes.

In the normal cat, the foot and four toe pads are soft, moist, and quite sensitive. However, after division of the sciatic nerve the foot and toe pads become hard and dry and frequently desquamate. During the time of heel drop, some of the animals have a temporary loss of hair on the plantar surface of the heel. However, in a small group of animals an ulcer appeared on the plantar surface of the heel by the second month and persisted until the animal was sacrificed even though this was 1 year after transplantation of the graft. Ulcers appeared in 12 per cent of the animals whose grafts were sutured with silk as compared to 9 per cent when the plasma clot technique was followed at operation.

RESPONSE TO DIRECT ELECTRICAL STIMULATION OF THE NERVE

At the time the animals were sacrificed, the nerve was electrically stimulated and the responses noted. Stimulation was performed with a stimulator designed by Hinsey and Geogehan which produced an alternating current of sine wave form with a frequency of sixty cycles per second and made it possible to measure the voltage necessary to produce a muscular contraction. The exposed nerve was stimulated with platinum electrodes at various levels, above, on, or below the suture lines and on the graft. The tibial and the common peroneal nerves were stimulated in the popliteal fossa and the tibial and the deep peroneal nerves at the level of the ankle. The reading of the voltmeter was taken when the stimulus was strong enough to produce a contraction. The amount of current needed to produce the responses varied between 0.01 and 0.9 volt, the average being 0.1 to 0.2 volt. The response was always more forceful when the current was applied at the suture lines than at the other points along the nerve in both

the grafts sutured with silk and those united with plasma. This situation is believed to exist because there is more likelihood of stimulating the naked axons at the suture line because of their lack of protective myelin covering.

The only response which was noted as early as 60 days was a weak contraction of the gastrocnemius muscle and this did not affect movement of the foot or toes. At 90 days, plantar flexion of the foot was present in 100 per cent of the animals whose grafts were united with plasma as compared to 75 per cent of those whose grafts were sutured with silk. However, at the same time plantar flexion of the toes was present in only 40 per cent of the animals whose grafts were united with plasma, while it was present in 50 per cent of the animals

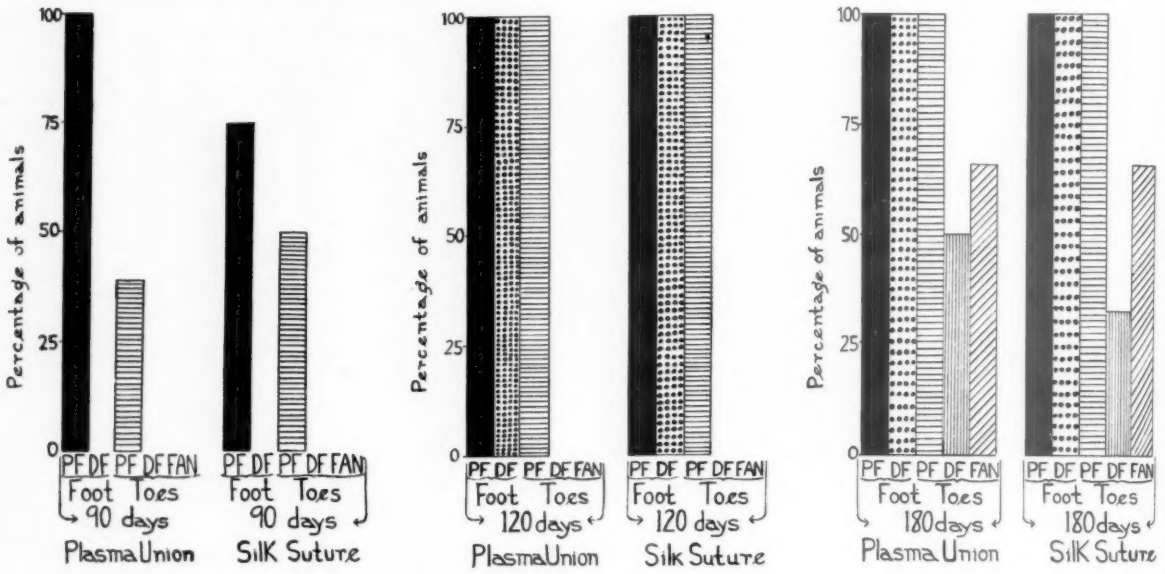

Fig. 1.—Responses of various muscle groups to direct electrical stimulation of the sciatic nerve 90, 120, and 180 days after transplantation of a homogenous graft. *PF*, plantar flexors; *DF*, dorsiflexors; *FAN*, abductors and adductors.

whose grafts were sutured with silk. At 120 days, plantar flexion of the foot, plantar flexion of the toes, and dorsiflexion of the foot were present in all animals regardless of the technique employed to place the graft. At 180 days, in addition to the motions observed at 120 days, 66.6 per cent of both groups had fanning of the fifth toe, and 33.3 per cent of the silk suture group had dorsiflexion of the toes as compared to 50 per cent for the group whose grafts were united with plasma (Fig. 1). At 1 year, motions were almost complete, but fanning of the toes was usually incomplete in that it involved only the fifth toe consistently.

The following motions were sought: plantar flexion of the foot, plantar flexion of the toes, dorsiflexion of the foot, dorsiflexion of the toes, and fanning of the fifth toe. If all five of these motions were found present the animal received a score of 100 per cent, while any four of these motions would yield a score of 80 per cent, etc. With these criteria, the cats whose grafts were united with plasma showed 28 per cent of the possible response at 90 days as compared to 25 per cent for the control group. At 120 days, the cats in both groups

showed 60 per cent of the possible response to electrical stimulation and at 180 days, the cats in the plasma clot group were capable of 83.2 per cent as compared to 80 per cent in the group whose grafts were sutured with silk (Fig. 2).

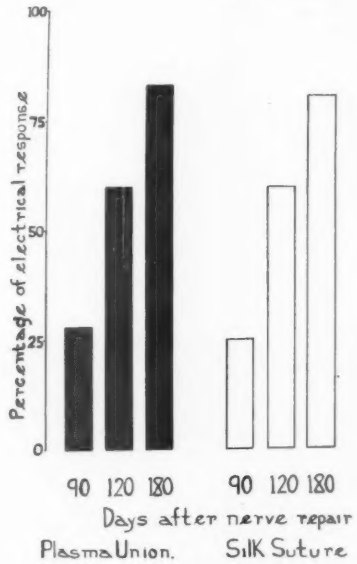

Fig. 2.—Average score of total muscular response to direct electrical stimulation of the sciatic nerve 90, 120, and 180 days after transplantation of a homogenous graft.

MUSCLE ATROPHY

Atrophy occurs in all muscles temporarily denervated. It reached its height at the second and third months when the muscles usually weighed 60 per cent less on the denervated side than on the normal side. The atrophy of the gastrocnemius and plantaris muscles exceeded the atrophy of the anterior tibial and extensor digitorum muscles. At 4 months, the return of weight to the muscles was apparent regardless of whether the graft was secured with plasma or with silk sutures, with a 41 per cent weight loss where silk sutures were used, as compared to a 37 per cent weight loss where plasma was used. At 6 months, the average percentage of loss was 31 per cent when the grafts were sutured with silk and 25 per cent when the grafts were united with plasma. At 1 year the atrophy was about 10 per cent regardless of the method used to place the graft.

GROSS APPEARANCE OF THE REPAIRED NERVES

The suture lines of the grafts were swollen in most instances. In the grafts sutured with silk, the distal suture line was often more swollen than the proximal suture line. The opposite was the case when the plasma clot technique was used; the proximal line of union being slightly thicker than the distal line (Fig. 3). Large amounts of adhesions surrounded the grafts and connected them with the surrounding tissues. The adhesions were always very vascular and the numerous blood vessels could be seen entering the epineurium of the grafts as well as the ends of the proximal and distal nerve segments. When the adhesions were freed, the surface of the epineurium of the graft was covered with small droplets of

blood. The epineurium of the graft was never as smooth and transparent as the epineurium of the normal nerve. At the time the animals were sacrificed, there was no indication of the presence of any plasma clot. Two of the grafts were completely surrounded by plasma at the time of operation to determine whether the surrounding blood vessels would penetrate the protective covering made by the plasma, and it was found when these animals were sacrificed 1 year later that there was no difference in the appearance of the grafts or their vascularization from the surrounding muscle bed. In the absence of silk sutures or other markings, it was impossible to determine accurately the site of approximation within the thickened line of union but the grafts which measured 2.5 cm. when placed did not appear to be longer or shorter when they were removed for examination.

Fig. 3.—Homogenous nerve graft 180 days after transplantation into the sciatic nerve. The proximal union is more swollen than the distal union.

MICROSCOPIC APPEARANCE OF THE REPAIRED NERVES

In spite of the care taken to section a nerve with a sharp razor blade and the caution exercised to place a nerve graft in apposition to the central and peripheral nerve ends with a minimum of handling, there was a traumatic zone within a few millimeters of the ends, more marked in the central than in the distal. The traumatic zone was characterized by debris, disintegration of myelin, and exudate. The result of the trauma was a proliferation of the endoneurium in the end of the central segment, and disorganized nerve fiber regeneration. Regeneration, however, proceeded and the proliferation of Schwann cells could be seen. Accompanying the Schwann cells were numerous fine axons. In the traumatic zone of the central segment, where there was an irregular proliferation of the mesodermal cells and an obstruction to the steady downgrowth of the axons by myelin decomposition products, numerous Perroncito spirals were found. A comparison between the nerves in which the grafts were united with plasma and those sutured with silk showed that frequently there was less exudate, debris, and fewer Perroncito spirals when the plasma clot technique was used,

but the appearance of the two groups of union was so identical that one could not distinguish whether the grafts were approximated with silk or with plasma.

The proximal point of union was characterized by a moderate proliferation of the perineurium and epineurium which continued over the graft. The structure inside the union showed considerable confusion of regenerating nerve fibers and mesodermal proliferation with minimal scar tissue formation. There was some deviation of the regenerating nerve fibers into the perineurium and epineurium. Study of the central line of union revealed an abundance of regenerated nerve fibers, many more than the original number of axons in the central segment from which these originated. However, the number of these fibers which passed directly into the fascicles of the graft was small, for many of the regenerating nerve fibers turned backward or penetrated the perineurium and epineurium of both the central segment and the graft. The distal union of the grafts resembled very much the proximal union except that there were no Perroncito spirals and even less perineural and epineural proliferation. Consequently, there was less nerve fiber deviation at the distal union.

The superficial layers of the grafts retained their viability, whereas the deeper areas often were necrotic. Where grafts were viable, the original fascicles were unchanged and the endoneural tubes remained. Regeneration of the grafts was always spotty but adequate in the peripheral layers. However, after the nerve fibers reached the distal segment, they were more numerous and uniform (Figs. 4 and 5). The advanced neurotization of the distal segment paralleled the greater absorption of the myelin decomposition products in the distal segment (Figs. 6 and 7).

At four months, axis cylinder formation was well advanced. The axis cylinders of the graft were beadlike (Fig. 8) while those of the distal segment were very uniform in appearance (Fig. 9). The difference corresponds to the marked mesodermal proliferation of the graft, for beadlike axis cylinders occur only where there is increased mesodermal proliferation as occurs in the junctions and the graft itself.

In a few animals, histologic examination of the sites of union revealed that there was a poor adaptation of the epineurium of the nerve segment to the epineurium of the graft and a large gap remained. At these points there was a great deal of confusion of the regenerated nerve fibers. The confusion always seemed greater at the central union than at the distal union. Most likely a mesodermal bridge was formed at the distal union before the nerve fibers crossed it. No correlation could be made between the confusion at the site of union and the neurologic findings of the animal. The distal segments always appeared well neurotized in spite of the wanderings of the nerve fibers at the sites of approximation.

HOMOGENOUS NERVE GRAFTS IN HUMAN BEINGS

It is agreed that end-to-end suture of severed nerves in man and animals is the method of choice. However, there are times when end-to-end suture is not feasible regardless of the methods employed to effect it, and the surgeon is confronted with the problem of bridging the defect. Autogenous nerve transplantation is generally accepted as a potentially successful procedure, but since

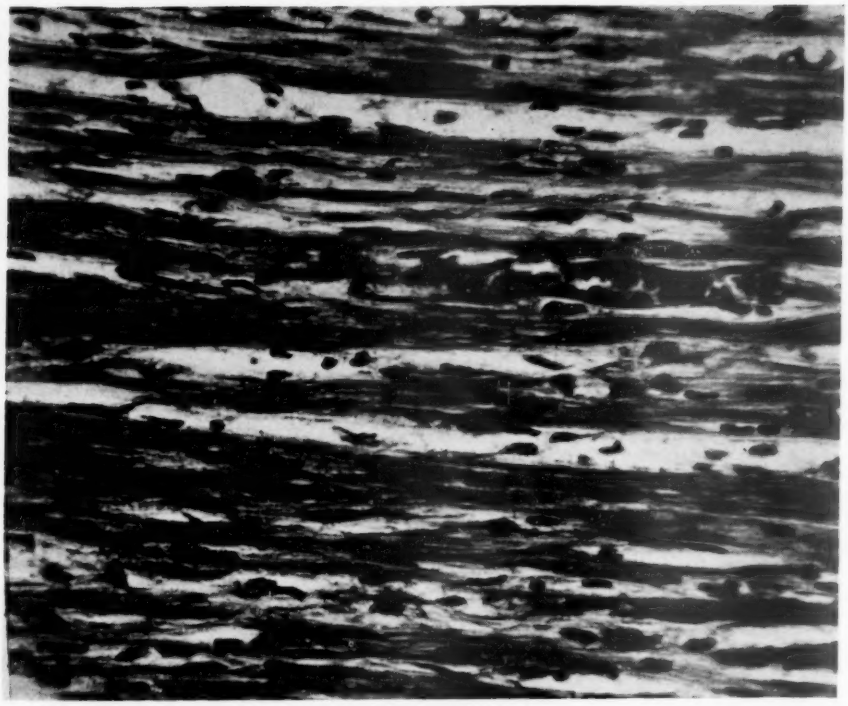

Fig. 4.—Homogenous nerve graft 60 days after transplantation. Regeneration of nerve fibers is not uniform. (Bodian fuchsin stain, ×450.)

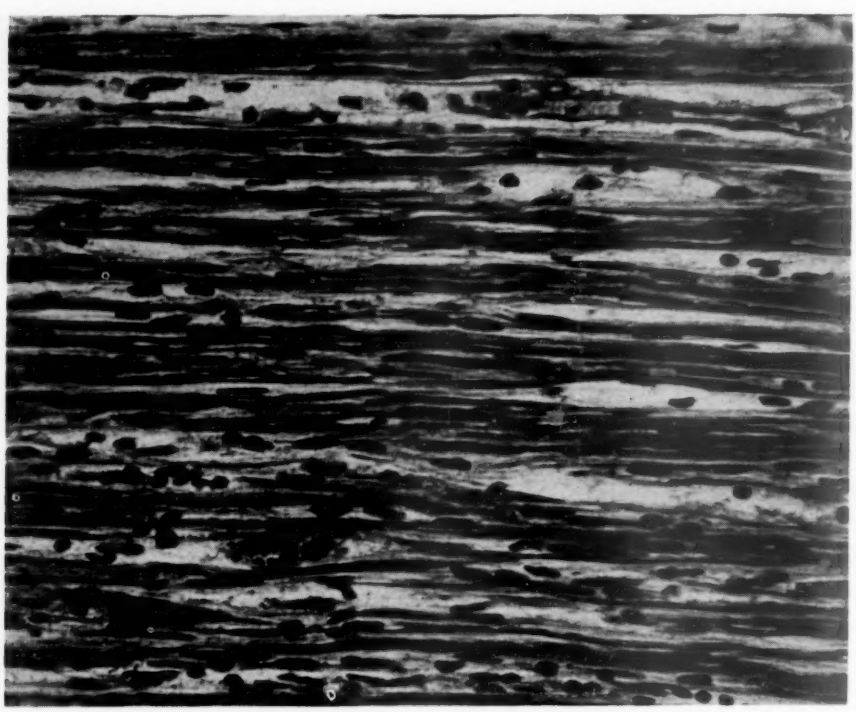

Fig. 5.—Distal segment of nerve 60 days after transplantation of homogenous nerve graft. Neurotization is more uniform in the distal segment than in the graft. (Bodian fuchsin stain, ×450.)

Fig. 6.—Homogenous nerve graft 60 days after transplantation. There is a great deal of myelin decomposition. (Weil stain, ×450.)

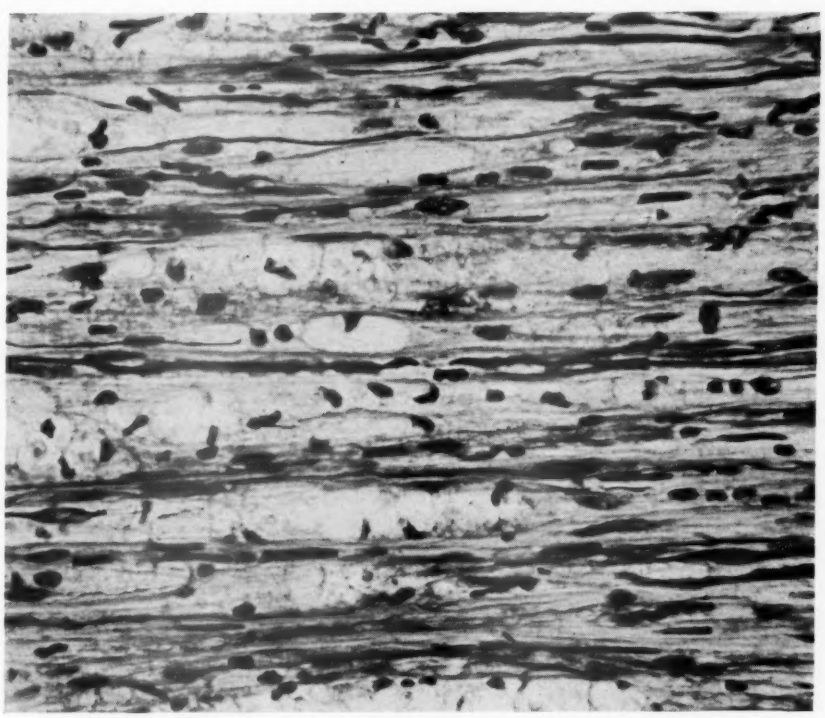

Fig. 7.—Distal segment of nerve 60 days after transplantation of homogenous nerve graft. Absorption of myelin decomposition products is farther advanced than in the graft. (Weil stain, ×450.)

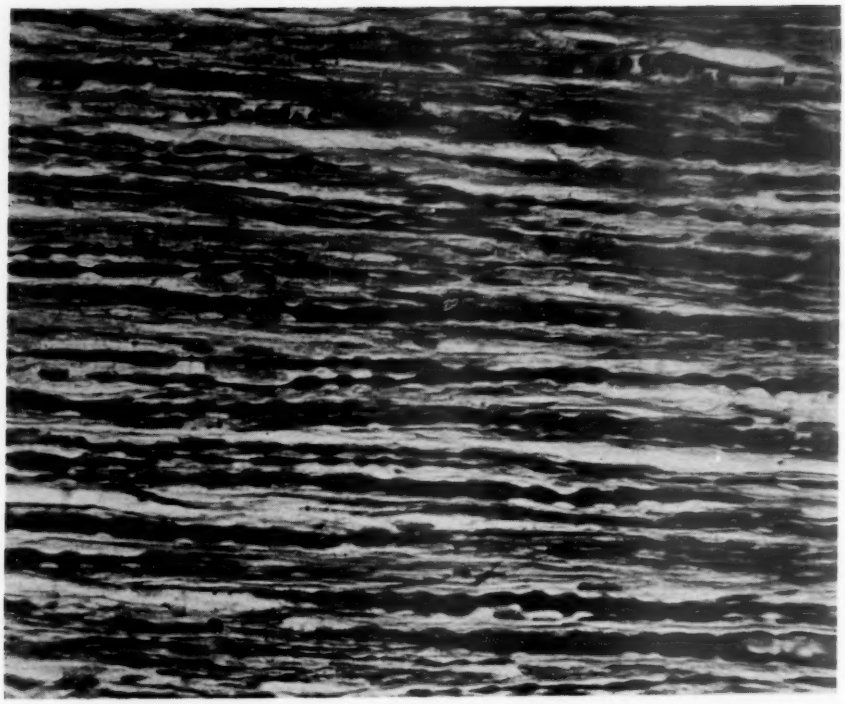

Fig. 8.—Homogenous nerve graft 120 days after transplantation. The axis cylinders are beadlike in configuration. (Bodian fuchsin stain, ×450.)

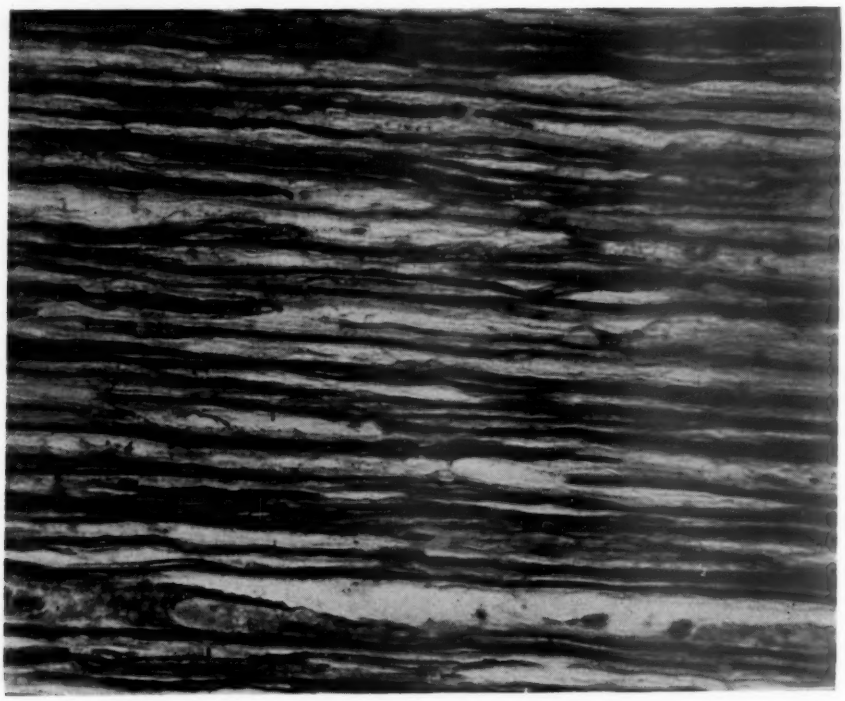

Fig. 9.—Distal segment of nerve 120 days after transplantation of homogenous nerve graft. Axis cylinders are quite uniform and free of constricting deformities. (Bodian fuchsin stain, ×450.)

it is often impossible, the surgeon has only the choice of a homogenous nerve graft. Many investigators have tried and discarded this procedure, maintaining that the graft produces a foreign body reaction in the host and is reduced to a fibrous band or is absorbed entirely.

Homogenous nerve grafts have been performed upon ten patients, who have been followed from 6 months to 16 years. The grafts were taken from the sciatic nerves of recently amputated extremities or from cadavers soon after death. They were obtained under strictly sterile precautions and were kept refrigerated for 30 minutes to 45 hours before being used. Fine silk sutures were employed in eight of the grafts and the plasma clot technique was used in the remaining two.

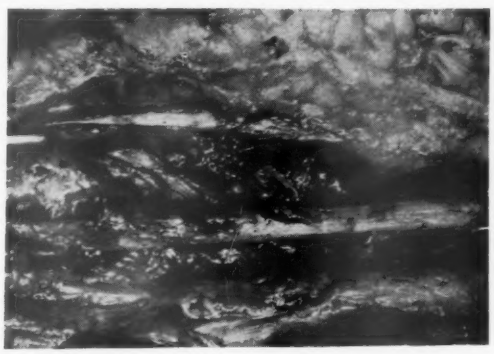

Fig. 10.—Homogenous nerve graft in a human being 127 days after transplantation. The graft has not been absorbed or reduced to a fibrous band.

While none of the patients has shown any return of motor function or enough evidence of regeneration to approach the normal, some have shown minimal evidence of recovery. For two patients it is too early to evaluate the results. Of the remaining eight patients, six have shown minimal evidence of recovery and two have shown no signs of regeneration.

Of those who have shown evidence of recovery, two received grafts to the radial nerve measuring 9 cm. and 12 cm. in length. Both have obtained perception to temperature, pinprick, and touch in the isolated area of supply of the radial nerve, but neither patient has shown motor recovery nor electrodiagnostic signs of neurotization. One patient has shown partial sensory recovery two years following transplantation of a 15 cm. graft to the peroneal nerve. Two patients who had grafts transplanted to the median and sciatic nerves have shown no sensory nor motor response, but electrodiagnostic studies show evidence of neurotization. One patient was admitted to the hospital 1 year following an injury to the right tibial nerve, totally disabled because of a chronic ulcer to the heel. Although there has been no demonstrable return of motor or sensory function, there has never been any recurrence of the ulcer in the 16 years since the 9 cm. graft was transplanted, and the patient has been able to continue his work as a farmer.

Three of the nerve grafts were exposed and examined 4 months, 4½ months, and 8 months following transplantation and in no instance had the graft been absorbed or reduced to a fibrous band (Fig. 10).

The functional recovery following the use of homogenous nerve grafts in man is markedly inferior to that obtained under experimental conditions in cats. Efforts should be directed toward simulating the latter in peripheral nerve surgery. Delay of months or years before a graft is transplanted permits the muscles to become severely atrophied and contracted, greatly limiting their function. The condition of the graft itself may be an important factor. In this experimental study the grafts were removed and transplanted immediately following the death of the donor, and the diameter and length of the grafts were smaller than those used in the human beings.

Previous experimental studies[7] have shown that recovery is slower in homogenous grafts than in end-to-end sutures. It is therefore suggested that in evaluating the results of homogenous nerve grafts in human beings more time be permitted than has been the practice; recovery if it does occur will be more delayed if a graft is needed to bridge the defect.

CONCLUSIONS

1. Plasma will hold divided nerve ends in apposition where there is no tension. It is suitable for grafts because tension can be easily avoided.

2. Motor response to direct electrical stimulation of the grafted nerves is the most objective sign of recovery. There is very little difference in the results obtained in the grafts united with plasma and those sutured with silk in cats.

3. Swelling is always present at the lines of union of homogenous grafts. When the plasma clot technique is used the proximal line of union is larger than the distal line. The regenerating nerve fibers cross the mesodermal bridge at the distal union without the wandering and resistance caused by debris which is resorbed at this point of regeneration.

4. Homogenous grafts are vascularized from the surrounding muscle bed. A protective covering of plasma clot placed around the entire graft and both lines of union does not prevent the ingrowth of small blood vessels.

5. The distal nerve segment always shows a successful neurotization regardless of whether the nerve fibers come to it via the nerve fascicles or via the perineurium and epineurium.

6. Functionally and microscopically there appears to be no advantage in using the plasma clot technique in preference to the silk suture method.

7. Experience with human homogenous grafts has shown that while the functional recovery is minimal, the nerve grafts are not absorbed or reduced to fibrous bands.

REFERENCES

1. Tarlov, I. M.: J. A. M. A. **126**: 741-748, 1944.
2. Young, J. Z., and Medawar, P. B.: Lancet **2**: 126-128, 1940.
3. Tarlov, I. M., and Benjamin, B.: Science **95**: 258, 1942.
4. Shapiro, A., Tarlov, I. M., Oliver, R., Goldfarb, A. I., Bojar, S., Kaslow, R., and Rockenmacher, M.: J. Lab. & Clin. Med. **29**: 282-295, 1944.
5. Tarlov, I. M., Denslow, C., Swarz, S., and Pineles, D.: Arch. Surg. **47**: 44-58, 1943.
6. Tarlov, I. M.: SURGERY **15**: 257-269, 1944.
7. Davis, L., Perret, G., Hiller, F., and Carroll, W.: Surg., Gynec. & Obst. **80**: 35-59, 1945.

FACIAL PAIN, PERSISTING AFTER RETROGASSERIAN RHIZOTOMY, RELIEVED BY MESENCEPHALOTHALAMOTOMY

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THE present methods for surgical treatment of trigeminal neuralgia such as Spiller-Frazier's retrogasserian rhizotomy or Sjöqvist's medullary tractotomy, sometimes fail to bring the expected relief despite properly placed lesions. These failures are due, in one group of cases, to the fact that one deals with "atypical pain" conducted to the central nervous system by way of spinal posterior roots instead of through the trigeminal nerve. In a second group, or combined with the first one, there may be a psychogenic, emotional factor causing a fixation of the patient's attention upon the pain area.

In cases of the first group, it may be indicated to combine interruption of the pain impulses of trigeminal origin and of those ascending from the spinal cord, chiefly in the spinothalamic tracts. Since these systems lie close together in the anterior part of the midbrain, they can here jointly be cut by a relatively small lesion.

Exposure of the midbrain by elevation of the posterior part of the cerebrum as carried out, for instance, by Walker[1] for mesencephalic tractotomy sometimes may cause considerable damage to the occipital lobe even in the hands of the most skillful neurosurgeon. By means of the stereotaxic technique developed by us,[2] this region may be reached easily, without the necessity of elevating the cerebrum: a fine needle electrode is introduced exactly at the desired coordinates of the skull, and the spinothalamic tract and/or the adjacent trigeminal systems may be destroyed by electrocoagulation or electrolysis with only minimal injury to the overlying cerebral structures.

In view of the existence of auxiliary pain conducting pathways, besides the previously mentioned chief systems, interruption of these main systems may also be insufficient to obtain complete relief, particularly if psychic factors are conducive to a persistence of the pain. Recently, Freeman and Watts[3] observed that, following prefrontal lobotomy, patients may become indifferent to various types of unbearable pain and thus receive a certain measure of relief. In some psychoses and obsessive-compulsive states, we were able to obtain, by medial thalamotomy[2] (lesion of parts of the nucleus dorsalis medialis thalami), similar beneficial effects as after prefrontal lobotomy, namely, relief from anxiety, tension, etc., but without many of the undesirable by-effects of the latter operation. Therefore, it also seemed justified to try thalamotomy, instead of prefrontal lobotomy, for treatment of unbearable pain. Accordingly, a combination of mesencephalic lesions of the long pain-conducting systems (Fig. 1) with medial

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thalamotomy[4] was developed. Both types of lesions can be produced by the stereotaxic technique, through a common trephine opening. An account of the first case in which this method of operation was used follows.

CASE REPORT

Mrs. J. D., aged 47 years, was admitted to Temple University Hospital on Sept. 16, 1947, because of severe pain in the region of the right temple. She was in apparent good health until November, 1940, when she developed a pain in the right side of the face. The pain started in the right lateral side of the face. She described it as being "lightning-like in character." Her local medical doctor made a tentative diagnosis of tic douloureux. The teeth were x-rayed and nine were extracted without relief. Sedatives, local heat, and inhalations of trichlorethylene were also tried without success. In April, 1941, another neurosurgeon relieved the pain for five weeks by a nerve block, but two subsequent injections did not relieve the pain. Subsequent to the nerve blocks she complained of a roaring noise in the right ear. In September, 1941, at another hospital, she underwent a retrogasserian root section, apparently by the conventional Spiller-Frazier approach. Following the operation, the pain became more severe and lasted for longer intervals of time. According to the patient a purulent discharge was present in the right eye following operation, and she wore a dressing over the eye for one month. When the dressing was removed, there was apparently an amblyopia ex anopsia. The pain persisted for seven years despite the use of analgesics. In September, 1947, the pain became more concentrated in the region of the right temple. Codeine, demerol, and morphine in adequate doses failed to alleviate the pain. Chewing aggravated it. Because of this difficulty there was a weight loss of eight pounds. There was a past history of tuberculosis.

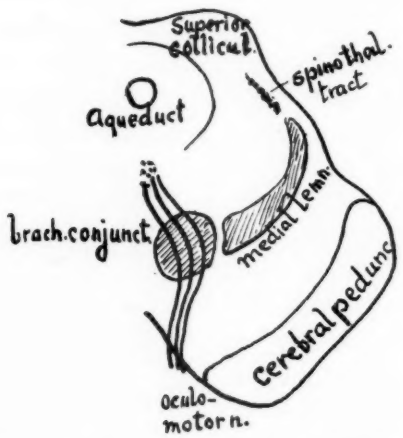

Fig. 1.—Schematic transverse section through the midbrain (modified after Marburg's Atlas) at the level of the superior colliculi, showing the postion of the long pain-conducting systems (spinothalamic tract). The pain-conducting trigeminal pathways lie close to, or are mixed with, the spinothalamic system.

Examination.—She was a thin, apprehensive individual who refused nourishment because of pain. She was confined to bed because of weakness and inanition. The general examination was essentially negative except for a diminution in visual acuity in the right eye. The right nasolabial fold was less pronounced than the left. There was a complete loss of all forms of sensation involving the right trigeminal field including the cornea. The temporal and masseter muscles on the right side were atrophied. There was difficulty in opening the jaws on account of the pain. A healed linear incision was visible in the right temporal region.

Preparation for Operation.—The patient was prepared for mesencephalothalamotomy in the following way: An x-ray picture of the skull was taken. A surgical defect was seen in the right temporal bone, and the pineal gland was visualized. A plaster cast of the skull was made, and the patient again x-rayed with the stereoencephalotome fixed to the cast and the needle in the zero position (at the intersection of the median and the interaural planes). The pineal gland was located 2 mm. behind the interaural line and 68 mm. below the surface of the cerebrum. From these data the levels and depths of puncture for coagulation of the spinothalamic tract, the secondary trigeminal pathways, and the dorsomedial thalamic nucleus were computed. The relative position of these areas in relation to the pineal gland was determined with the aid of specimens sectioned in the frontal plane of the stereoencephalotome.

Mesencephalothalamotomy.—Oct. 30, 1947, with the plaster cast in position, a trephine opening was made over the superior longitudinal sinus under local anesthesia. The superior longitudinal sinus was exposed. The stereoencephalotome was applied to the plaster cast and electrocoagulation was produced by means of the Bovie-Flarsheim apparatus. Three punctures (five lesions) were made in the region of the left dorsomedial nucleus of the thalamus and two punctures (four lesions) were made in the region of the left spinothalamic tract and secondary trigeminal pathways at the level of the superior colliculus.

Postoperative Course.—Two hours after operation the patient volunteered the information that the pain had entirely disappeared. She stated that the right hand and leg felt different from the left and were numb. There was a moderate impairment in movement of the right toes and ankle. There was an impairment of sensation to pinprick, heat, cold, and, to some extent, also to light touch over the entire right side of the body below the face. The face was anesthetic from the previous trigeminal nerve operation.

On the fifth postoperative day a better evaluation of her neurological status was obtained. She was completely free of pain. She could now enjoy food, and her appetite was considerably improved. There was a slight paresthetic sensation of the face which she described as a "zig-zag flash" in the right upper lip. This did not annoy her and occurred at irregular intervals. The right nasolabial fold was slightly less pronounced than the left. Neither the voluntary innervation of the right facial muscles nor their involuntary reaction, for example, in laughing, was more impaired on the right than on the left side. The grasp was not definitely impaired on the right side. A Hoffmann sign was not elicited. The movements of the right toes and ankle had improved so that now only a very mild impairment in these movements was noted. There was ankle clonus on the right and fanning of the toes on plantar stimulation, but a Babinski sign could not be elicited. Plantar stimulation was better tolerated on the right side. Pain, heat, and cold sensation were markedly diminished on the right side but not totally lost. The hypalgesia nearly reached the midline (Fig. 2). Light touch sensation (to cotton wool) was slightly affected on the right side except the medial aspect of the right thigh which was more sensitive to all forms of stimulation. Vibration sensation was impaired in the right upper and lower extremities. Position sensation was unimpaired except in the large toe of the right foot. She could recognize downward but not upward movements of this toe.

Wound healing was satisfactory. She was out of bed on the third and discharged on the ninth postoperative day. She was free of all pain and able to walk about and feed herself. The roaring noises in the right ear had ceased. On the day of discharge, the findings were similar.

On Nov. 18, 1947, the patient reported an increase in weight of one pound within the past ten days; she admitted occasional sensations like electric shocks around the right eye, but insisted that she was free of pain. There was hypalgesia of the right hand, no definite difference between left and right in the reaction to touch or vibration; no definite difference in the deep reflexes of the arms; motor power of the hands equal. There was a very slight bilateral intentional tremor, but no resting tremor. On holding objects such

as a large test tube, there was a slight tremor, more pronounced in the right hand than in the left. The right patellar reflex was slightly more active than the left; there was no definite increase of the right Achilles reflex, no ankle clonus, no disturbance of the deep sensation or of vibration sensation in the right lower extremity. In standing and walking, there was a slight tendency to tilt to the right side.

On Dec. 16, 1947, there was still a hypalgesia on the right lower arm and the tip of the fingers. There was no longer a definite impairment of the sensation to cold or warm in the hands, but a slight diminution in the right dorsum pedis.

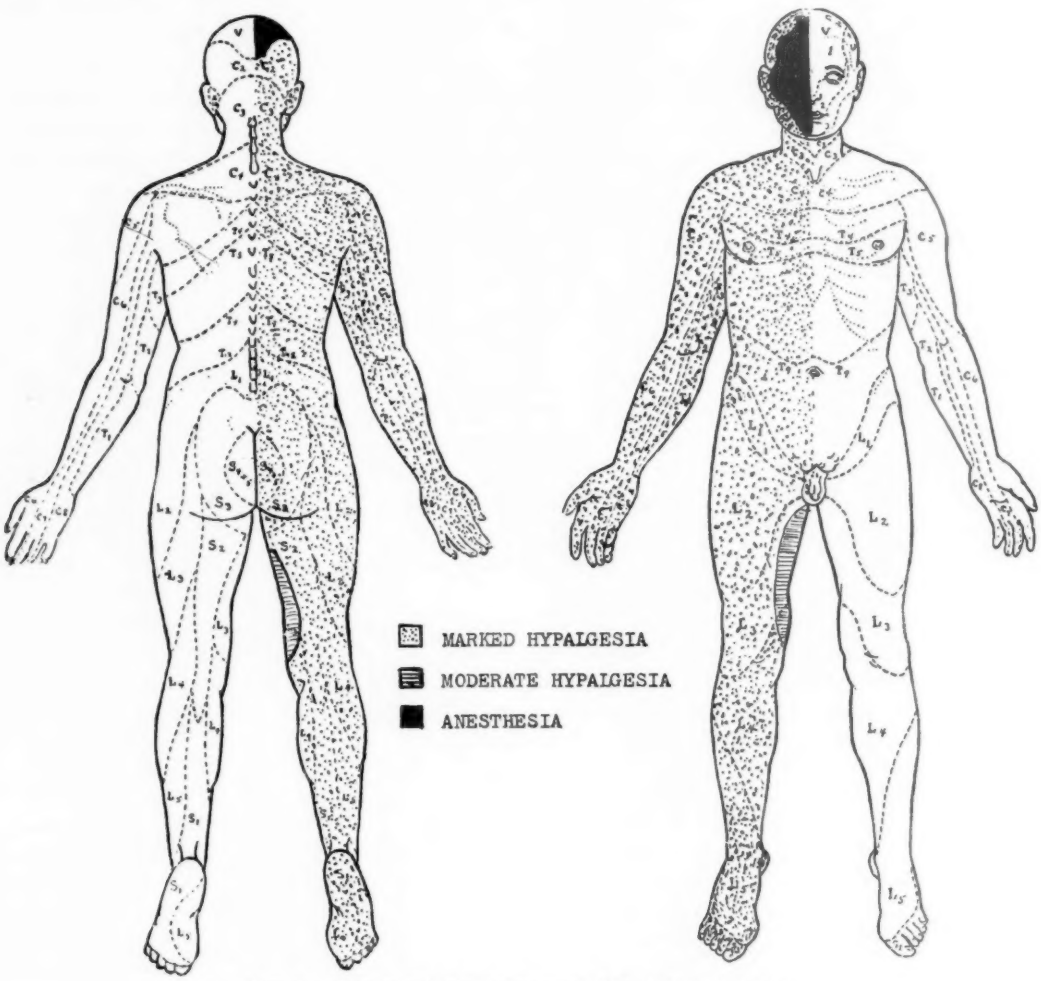

Fig. 2.—Sensory disturbances of J.D., Nov. 4, 1947.

Feb. 18, 1948, the patient had resumed work in her household one month previously. She was still completely free of all pain. The right pupil was slightly smaller than the left and there was a mild enophthalmus on the right side (mild Horner's syndrome). The corneal reflex was absent on the right side. The right side of the face was anesthetic to all forms of sensation; this sensory loss did not extend sharply to the midline. Audiometric examination showed hearing to be normal bilaterally. The gait was normal. The dynamometer reading on the right side was 15 and on the left 13. There was a mild tremor on holding objects, this being more pronounced on the right as compared with the left hand. There was no ataxia on the finger-to-nose or the heel-to-knee tests. The routine cerebellar coordination tests were performed without difficulty bilaterally. Motor power in the lower

limbs was equal bilaterally. The deep tendon reflexes were active and equal. Hoffmann, Babinski, and Oppenheim signs could not be elicited. Vibration and position sensation were unimpaired and equal on both sides. Deep pressure on the ulnar and peroneal nerves elicited pain equally on the two sides. The former hypalgesia to pinprick below the face area on the right side had retrogressed and now pinprick was felt on the two sides except for an elongated oval area over the anterior aspect of the right thigh, which was still analgesic. However, there were still quantitative differences in pain sensation between the right and left side as demonstrated by an algesimeter; for example, in the right finger tips the threshold values were higher than on the left side. Two point discrimination tests showed no apparent differences on the two sides (excluding the face). Tactile localization was slightly impaired on the right; for example, on the right forearm the average error was about 1 cm. larger than on the left. Skin writing was well perceived bilaterally.

May 25, 1948, impairment of tactile localization was still demonstrable on the right side; for example, on the right upper arm the error was 4 to 5 cm., on the left 2 to 3 cm. There were also errors in the distinction of a pin and a hair on the right arm. For the demonstration of residual disturbances of sensation on the right side, examination with Von Frey* pins proved very valuable; for example, with a pin of 0.4 Gm. pressure 40 stimulations of an area of 1 sq. cm. revealed eight pain points in the right and twenty points in the left fossa cubiti.

Dec. 21, 1948, the patient was still free of pain.

The question may be raised whether this case should be classified as a true "idiopathic" trigeminal neuralgia or as an "atypical" or psychogenic form. We did not have an opportunity to see the patient in 1941 preceding the first operation. However, the fact that the retrogasserian rhizotomy was performed by a neurosurgeon known for his experience in hundreds of cases of trigeminal neuralgia seems ample proof that the patient presented at that time a picture justifying the Spiller-Frazier operation, that is, the picture of an idiopathic trigeminal neuralgia. There can also be no doubt that the root of the trigeminal nerve had been properly cut, since this operation was followed by the development of the typical complete anesthesia in the area of the fifth nerve.

The persistence and even increase of the pain following the correctly performed rhizotomy may, at least partly, be due to the formation of scar tissue caused by alcohol injections into the region of the gasserian ganglion and/or by the rhizotomy. This scar tissue may have irritated meningeal nerve fibers at the base of the skull.

The existence of a psychogenic, emotional factor is suggested by the development of an amblyopia in the right eye. It should also be mentioned that the patient was emotionally unstable when first seen by us in 1947. However, this should not appear surprising in a patient suffering for many years from severe pain, and should be regarded as the consequence rather than the cause of the pain, particularly since the patient appeared emotionally well balanced on repeated examinations following relief from the pain by the mesencephalothalamotomy. Thus we are inclined to consider the emotional component in this case as superimposed upon the original picture, and not as the chief cause of the pain attacks.

*We wish to express our sincere thanks to Professor v. Ackermann, Würzburg who kindly sent us a set of original v. Frey hairs and pins.

The mesencephalothalamotomy was performed unilaterally on the side contralateral to the pain area, since it seemed advisable to ascertain whether the unilateral operation would be sufficient, and to add the operation on the homolateral side at a later date, if indicated. This proved to be unnecessary, and the patient remained free of the pain attacks during an observation period of fourteen months. The only abnormal sensation reported by the patient upon inquiry were occasional paresthesias, "zig-zag flashes" in the right cheek and around the right eye. We were particularly interested to ascertain whether the unilateral thalamotomy was responsible for the fact that the patient mentioned these occasional paresthesias upon inquiry only, in other words, whether an indifference to the pain similar to that observed after prefrontal lobotomy (Freeman and Watts[3]) played a part after the mesencephalothalamotomy. This question can hardly be decided in this case, since the remaining paresthesias were too slight, according to the patient, to cause real discomfort.

The question may be raised whether the spinothalamic tract was injured by the electrocoagulation. The development of hemihypoesthesia for pain and temperature permits this question to be answered in the affirmative. The existence of a complete anesthesia in the right trigeminal area due to the rhizotomy precluded an answer to the question whether the electrocoagulation had also affected the trigeminal pathways in the midbrain. The observation that the hemihypalgesia initially nearly reached the midline is in agreement with Walker's[1] experiences after mesencephalic tractotomy. It seems particularly of interest that the hemianalgesia regressed considerably, probably due to incomplete interruption of the spinothalamic system, and/or to compensatory functioning of auxiliary pathways, while the pain attacks did not recur. A satisfactory explanation of this development cannot be given at the present time, but only a hypothetical one; it may be assumed that a vicious circle existed: the pain inducing vasospasms, and these in turn aggravating the pain, and that the operation interfered with this vicious circle.

Regarding by-effects of the operation, there was a transitory impairment of the mobility of the right toes and ankle, apparently because the needle of the stereoencephalotome passed through the paracentral lobule in order to reach the dorsomedial nucleus of the thalamus. The transitory slight disturbances of sensation to touch, deep sensation, and tactile localization, as well as the transitory tremor, particularly of the right hand, apparently are due to the fact that the focus of coagulation produced by the high-frequency current in the area of the spinothalamic tract was surrounded by a zone of slighter impairment, including the medial lemniscus (Fig. 1) and the brachium-conjunctivum-ruber system, an impairment that was so slight that these systems recovered in a short time. These transitory by-effects were negligible compared with the relief from severe pain of many years' duration.

It would be premature to recommend this method as a standard method for treatment of unbearable pain, the purpose of this presentation being only to demonstrate the possibilities of the stereotaxic method in this field.

SUMMARY

A case of trigeminal pain is described. It persisted for seven years (six years after retrogasserian rhizotomy) and was completely relieved by combined electrocoagulation of the pain-conducting systems in the mesencephalon and of the dorsomedial nucleus of the thalamus by means of the stereotaxic technique (mesencephalothalamotomy; time of observation after operation, fourteen months).

REFERENCES

1. Walker, E.: Relief of Pain by Mesencephalic Tractotomy, Arch. Neurol. & Psychiat. **48:** 865, 1942.
2. Spiegel, E. A., Wycis, H. T., Marks, M., and Lee, A. J.: Stereotaxic Apparatus for Operations on Human Brain, Science **106:** 349, 1947.
3. Freeman, W., and Watts, J. W.: Pain of Organic Disease Relieved by Prefrontal Lobotomy, Lancet **1:** 953, 1946.
4. Spiegel, E. A., and Wycis, H. T.: Mesencephalotomy for Relief of Pain. Principles of the Method. In Anniversary Volume for O. Poetzl, Vienna, 1948, p. 438.

PROGRESS IN CORRECTION OF FACIAL PALSY WITH TANTALUM WIRE AND MESH

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THE use of tantalum to support the face in facial paralysis has greatly simplified correction of the deformities attendant on this condition. No longer is it necessary to draw upon the patient for fascial strands to supply traction. The procedures by which the supporting wire or ribbon is inserted are simple and relatively free from risk. As only slight trauma is inflicted, the postoperative reaction is proportionately mild and the period of hospitalization brief.

EARLIER PROCEDURE

Early methods to raise the mouth with tantalum wire employed three loops affixed to the temporal muscle.[1] Under local anesthesia a curved incision two inches long was made over the temporal muscle above the zygoma, exposing the temporal fascia. A long curved 18 gauge Weck needle was inserted in the lower part of the incision and passed downward between skin and mucosa (taking intermittent bites of each) to emerge 8 mm. beyond the midline of the chin. After threading with tantalum wire or ribbon, this was withdrawn, carrying the metal back with it to the temporal incision. The loop was completed by inserting the other end of the wire in the bore of a needle paralleling the course of the first 1 cm. above it. A vertical incision between the upper and lower wires on the chin received the center of the loop, around which tantalum foil was wrapped to prevent tearing of the underlying tissues. By the same procedure a second loop was affixed 0.5 cm. from the corner of the mouth. Still a third, on the upper lip, was formed by a lower wire following the course of the vermilion border to 6 mm. past the midline and an upper one running just below the base of the nose to raise any sagging there. The three sets of wire in the temporal incision were then pulled taut to overcorrect the face slightly. The ends of each pair were twisted together and embedded deeply in the temporal muscle and fascia (Fig. 1).

The same principle was applied to the support of the upper eyelid. Bearing a needle of shorter design, a carrier inserted at the upper part of the temporal incision was advanced under the upper orbital rim, downward and forward, to emerge over the attachment of the internal lateral ligament (Fig. 2). A second needle, inserted 1 cm. below, followed the course of the lower lid, issuing beneath the attachment of the internal lateral ligament. A vertical incision between the two needles permitted the loop formed by threading them to be moored in the ligament. After this set of wires was pulled taut and affixed, the temporal incision was sutured.

This method yielded predominantly good results in approximately sixty cases, military and civilian, in which it was employed (Fig. 3). In about 35 per cent, the results left little to be desired. In an equal number the facial

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distortion was greatly improved but some lagophthalmos persisted. The remaining 30 per cent showed no appreciable improvement, mainly because of mechanical failure of the wire.

Fig. 1.

Fig. 2.

Fig. 1.—Before operation. Note condition of lagophthalmus, deformity in temple area produced by a former surgical intervention, and nasal twist.

Fig. 2.—After operation. Note correction of lagophthalmus, improvement in the temple area, and straightness of the nose.

Fig. 3.

Fig. 4.

Fig. 3.—Front view after operation.

Fig. 4.—Needle carrying wire, inserted through one of the facial tracts.

While the wire proved biologically inert and remained embedded in the tissues without inflammatory reaction, sometimes it sagged or broke and had to be tightened or replaced. Although this was a simple matter, not requiring hospitalization, it spurred the search for a stronger supporting material.

Schuessler[2] abandoned the use of tantalum wire because of adverse experience with multiple breaks.

Occasionally a wire had to be removed because its presence in the adjacent tissues could be felt in the mouth; apparently greater flexibility was also a desideratum. Above all, the surgical technique seemed unnecessarily complicated.

NEW PROCEDURE

The following method promises to overcome most of these objections. While it has been used in too few cases for final judgment, it is gratifyingly simple and appears to achieve its objectives more effectively than the technique already described. The use of braided double tantalum wire provides a firmer and more supple supporting material: one loop does the work of three previously employed to raise the mouth; and to date the double braided wire has never broken. Application of a simple mechanical principle overcomes the lagophthalmos without the use of any loops at all.

Support of Mouth.—After outlining of the incisions, the surgical area is infiltrated with 2 per cent Novocain and adrenalin hydrochloride. The first incision, in front of the ear, starts just below the tragus and extends upward into the hairline for 2½ inches. Wide undermining gives access to the face. A second incision of similar length is begun about one-half inch below the angle of the mouth and carried upward in a curved line in the site of the obliterated nasolabial fold. The proximal skin is undermined for about one-quarter inch.

A needle carrier inserted into the lower part of the temporal wound is advanced to the lower part of the nasolabial incision with a weaving motion, biting alternately into the skin above and the tissues below. On emerging in the nasolabial incision, it is threaded with braided No. 1 double tantalum wire. The carrier is then retired through the temporal wound, carrying one end of the wire braid with it. This procedure is repeated with the carrier entering the upper part of the temporal wound and issuing at the corresponding portion of the nasolabial incision. The second needle is threaded with the other end of the strand of tantalum braid. To provide firmer anchorage and prevent the wire from damaging the tissues as it is drawn into the wound, the loop formed by the retirement of the second carrier is reinforced with tantalum gauze. The ends of the wire are then pulled taut and attached to the aponeurosis of the temporal muscle in generous bites (Fig. 4).

Correction of Lagophthalmos.—To correct the lagophthalmus, a small inverted V-shaped incision is made in the center of the upper lid, near the outer canthus. The surrounding skin is undermined to create a sulcus close to the orbital ridge. Into this a strip of tantalum gauze, two inches long and of six-fold thickness, is inserted. After fitting of the mesh into the desired position, the eyelid wound is closed. The slight weight of the tantalum pad provides sufficient antagonism to the pull of the levator muscle to permit closing of the

eye. Mesh is used instead of a solid metal form as the surrounding tissue eventually penetrates its openings, ensuring permanent immobilization.

Repair of Temporal Defect.—Where previous attempts at repair with muscle transplants have left a temporal defect, the latter can be filled out with tantalum gauze, folded as often as indicated, and cut to pattern. This is inserted before closure of the temporal incision.

COMMENTS

These procedures do more than raise and stabilize the face and enable the eye to be closed. They also mitigate the most characteristic secondary deformities of facial paralysis.

When the nasolabial wound is sutured, the relaxation on the proximal side and stability on the distal side combine to produce a sort of introversion of the skin simulating the absent nasolabial fold. In addition, as the mouth is opened and closed, the pull on the wire at its temporal attachment gives the semblance of motion in the cheek.

Still another improvement is the fullness of the face achieved as tightening of the wires pulls the tissues together. In combination with the re-establishment of the nasolabial fold, this serves to mitigate the flatness of the cheeks resulting from the muscular atrophy in facial paralysis.

In a report on two cases repaired by tantalum-wire suspension, Schultz and Fowler[3] complained of a subsequent tendency of the paralyzed cheek to balloon out during speech. Judging by personal experience, such distortion is temporary, disappearing as the organs of speech adjust to the new contours.

The same authors also commented on the difficulty of maintaining dentures in position after this method of repair. However, there are many methods of adjusting and affixing the prosthesis to overcome this objection. At most the patients are rendered temporarily toothless for a very short time.

In connection with the use of tantalum wire saddles, Schultz and Fowler warned of the latter's tendency to cut through the muscle bundles. This hazard is preventable by the use of tantalum gauze, as described, to reinforce the loop at its affixation to the lip.

All in all, the objections adduced are slight compared to the substantial advantages gained. However, patients seeking this type of correction should be advised of the possible need for adjustment of the wire from time to time.

REFERENCES

1. Sheehan, J. E.: Unilateral Facial Paralysis; Correction With Tantalum Wire; Preliminary Report on Eight Cases, Lancet **1**: 263, 1946.
2. Schuessler, W. W.: Personal oral communication.
3. Schultz, L. W., and Fowler, E. F.: Treatment of Facial Paralysis by Tantalum Wire Suspension: Preliminary Report, Plastic & Reconstr. Surg. **2**: 538, 1947.

ESOPHAGEAL DILATATION: A CONTRAINDICATION TO THE SWALLOWED THREAD, AND AN ALTERNATIVE METHOD

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TODAY great strides are being made in definitive surgery of the esophagus. Nevertheless, instrumental dilatation of strictures of the esophagus still retains a place in the armamentarium of anyone who concerns himself with this organ. In such dilatation the primary hazard is that a false passage with perforation may be made in the dilated, thin-walled esophagus proximal to the stricture. Various methods have been devised in an effort to prevent this. These are principally dilatation under direct esophagoscopic vision (Jackson[2]), the use of catheters weighted with lead shot or mercury (Bokay[1]), and the use of a swallowed silk thread as a guide.

Though all three methods have their indications, the use of a silk thread has proved satisfactory for most cases in our hands. Von Hacker[7] in 1894 suggested the swallowing of a string, fishing of the latter out of a gastrostomy opening, and dilation of strictures by attaching bougies to this distal end and pulling them up retrograde. This method of retrograde bouginage was later emphasized by Tucker.[5] We prefer not to make a gastrostomy purely for the purpose of dilatation; though, if a gastrostomy is already present, such a procedure utilizing traction, rather than pulsion, is probably safer. Mixter[3] in 1909 showed that, without a gastrostomy, a silk thread may be swallowed and, if enough thread passes (4 yards or more), will become "anchored" in the intestines so that peroral dilatation may be done over the taut thread as a guide. This procedure has been publicized by Plummer[4] and Vinson.[6] We use Plummer's sounds modified by Vinson with silk thread (usually size D buttonhole twist) as a guide. If this method is used correctly, it is a safe procedure.

Vinson[6] in 1931 pointed out that should a fistula exist between the esophagus and the bronchial tree, the swallowed thread may pass into the trachea, be coughed up and re-swallowed ad infinitum until a constrictive band exists about the pharyngoesophagotracheal circle which may cause laryngeal edema necessitating tracheotomy. Vinson also mentioned that if a gastroenterostomy is present, the swallowed thread may pass repeatedly about the gastroduodenojejunal circle. At that time he wrote, "Theoretically it may produce mechanical difficulties; I have never seen any serious results, although the thread has been used many times under similar circumstances."

As recently stated by Wangensteen,[8] our experience at this clinic does not lead to as complacent an attitude. We have observed two instances where silk thread was swallowed in the presence of an enteroenterostomy. Both cases

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terminated fatally, at least one of the deaths being directly caused by the swallowed thread. The latter case will be reported in some detail, the other more briefly.

CASE REPORTS

CASE 1 (F. C., U. H. No. 763504).—This 72-year-old white male was operated upon on March 13, 1946, for a huge scirrhous carcinoma involving the entire stomach and the lower 6 or 7 cm. of esophagus. A total gastrectomy was performed including the lower 7 to 8 cm. of the esophagus and the spleen. An esophagojejunostomy was made, bringing the jejunum up as a loop, with an enteroanastomosis being performed between the two limbs of jejunum.

The immediate postoperative course was uneventful. About the tenth postoperative day, however, the patient began to have difficulty swallowing. Therefore, on March 25, 1946 (thirteenth postoperative day), the patient was given a spool of size D, buttonhole twist silk thread to swallow. On March 26, 1946, esophageal dilatation was unsuccessful since the thread broke; therefore, the patient began swallowing another thread. The next day esophagogram revealed no constriction at the anastomosis, so the thread was cut in the mouth, the patient swallowing that which remained in the pharynx.

From this time on, the patient continued to vomit most of what he attempted to swallow. On April 7, 1946 (the twenty-fifth postoperative day), he vomited 200 c.c. of fresh blood, and later passed a large tarry stool in which was imbedded a ball of thread similar to that previously swallowed. Though he was sustained on transfusions, hemorrhage continued and on April 16, 1946, laparotomy was performed. It was thought that the thread was wound about the loop formed by the enteroenterostomy and had caused ulceration of the mucosa and hemorrhage, and it was planned to open the bowel and cut the thread. However, adhesions were so dense and vascular and the patient's condition so precarious that this procedure could not be carried out. A side-to-side duodenojejunal anastomosis was done instead, by passing the old enteroenterostomy. Postoperatively, the patient continued to vomit blood and to pass tarry stools. In spite of vigorous replacement therapy, he died on April 19, 1947, having been given 6,000 c.c. of blood in the previous seventy-two hours.

Pertinent findings at autopsy were as follows: The entire intestinal tract was filled with blood. Several loops of thread were wound around the loop of jejunum enclosed between the esophagojejunostomy and the jejunojejunostomy. The mucosa beneath this thread showed evidence of erosion and ulceration, and it appeared that there had been erosion of the underlying vessels. No other site of bleeding was found in the entire gastrointestinal tract.

CASE 2 (F. B., U. H. No. 709658).—This patient, a 43-year-old white male, likewise underwent a total gastrectomy for carcinoma of the stomach on July 5, 1941. An esophagojejunostomy was made, utilizing a loop of jejunum with an enteroanastomosis between the two jejunal loops. He was discharged from the hospital on July 21, 1941, after a smooth postoperative course, and returned to the clinic on Aug. 6, 1941, having swallowed approximately 6 yards of size D buttonhole twist silk thread. A size 45 French Plummer sound was passed easily through the anastomosis and the thread was then cut at the mouth, the patient swallowing the free end. His course continued uneventful until Aug. 17, 1941, when there was an onset of anorexia, epigastric distress, hiccoughs, and vomiting. He was readmitted to the hospital on Aug. 24, 1941, on which day a Miller-Abbott tube was inserted. On Aug. 27, 1941, laparotomy was performed; generalized carcinomatosis was found, and a sidetracking procedure about an obstructed loop of bowel was made. On Sept. 1, 1941, attempts to remove the Miller-Abbott tube were unsuccessful, in spite of esophagoscopy and another laparotomy. Following this latter operation, the patient did quite well for a week or two, only to then start a downhill course, expiring on Oct. 5, 1941.

At autopsy the swallowed silk thread was found to be wrapped around the loop formed by the esophagoejunostomy and enteroenterostomy. The Miller-Abbott tube was inextricably entwined in several strands of this thread. Other significant findings were generalized carcinomatosis of the peritoneal cavity with multiple areas of involvement of the upper small bowel.

On the basis of these two cases we feel that the use of the swallowed thread is contraindicated in the presence of an anatomic loop in the alimentary tract, whether it be an enteroenterostomy, gastroenterostomy (with patent duodenum), or esophagotracheal fistula.

Three years ago, one of us (N. L. L.) utilized a form of esophageal dilatation that does not necessitate the swallowing of a string. This method utilizes the principle of the filiform and follower as employed by urologists in urethral dilatation. Following primary esophageal anastomosis for congenital tracheoesophageal fistula in infants, dilatation was sometimes necessary for recurrent stricture at the site of anastomosis, and in other cases prophylactic dilatation was thought advisable. These cases have been dilated with uniform success by means of Phillips urethral filiforms and followers (filiforms, size 2 to 6 French). Since first used in September, 1946, sixty-three such dilatations have been done with the formation of no false passages or other untoward results.

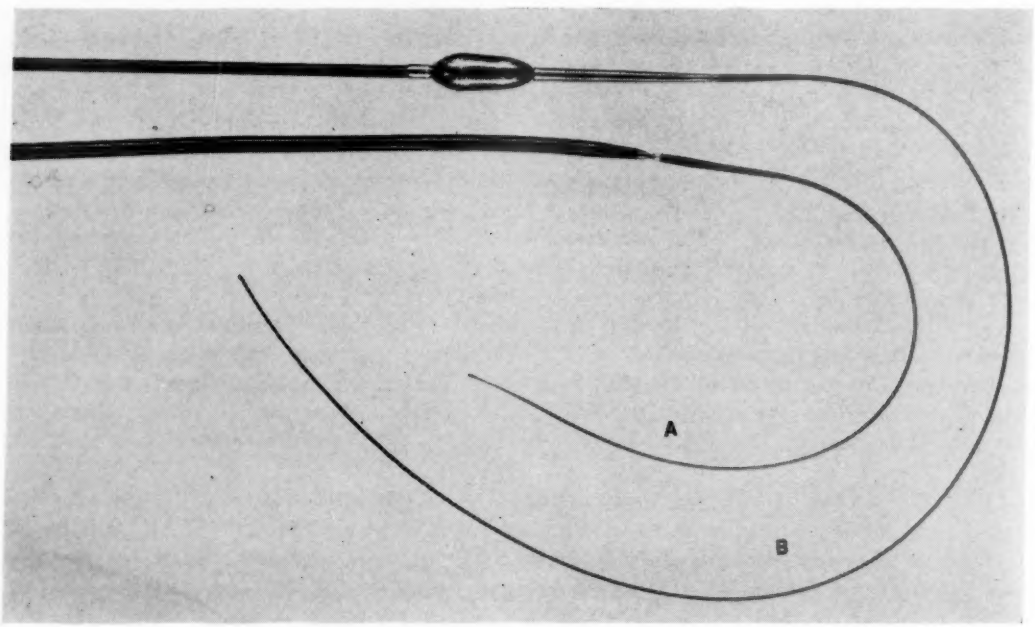

Fig. 1.—*A*, Filiform and follower as used in infants. *B*, Plummer sound with attached radiopaque filiform as used in adults.

Since these strictures are relatively high in the esophagus, we have usually felt confident of the "feel" of the filiform and have dilated without radiologic control. More recently, however, we have had made radiopaque filiforms.* Passage of the latter with fluoroscopic control certainly adds to the safety of the procedure, and likewise is an aid in passage through the more severe stricture. In regard to the latter, it should be noted that there has been an occasional stricture which, while impermeable to a straight-tipped filiform, has been successfully passed with a filiform with a corkscrew tip.

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In adults, especially in strictures located at some distance from the mouth, one cannot rely on tactile sense. For use, therefore, in those esophageal dilatations in adults where a swallowed thread cannot be used, a woven silk filiform (size 4 French) has been devised that is 50 cm. long and that is radiopaque.* This has been joined to the Plummer sound by means of a male screw attached to the tip of the latter.† The Plummer dilator is easily visible under the fluoroscope, as is the filiform. Under radiographic control, the filiform is passed until its tip lies in the stomach. The dilator is then passed, it being noted under direct vision that the filiform does not buckle as it lies in the esophagus, but merely curls up in the stomach (Fig. 1).

It is not suggested that this method of dilatation should replace the use of the swallowed thread in adults. The use of the fluoroscope adds time and expense to the procedure, and repeated fluoroscopy in long-term cases would be unwise. Moreover, its safety has not been proved in a large series of cases. Nevertheless, the few cases in which this procedure has been tried suggest that it is both a safe and useful alternative in those adults who either cannot or should not swallow a thread. In infants, however, in whom it is often not feasible to utilize a swallowed thread, the use of the filiform and follower is of primary value.

SUMMARY

The use of the swallowed thread for esophageal dilatation is contraindicated in the presence of an anatomic loop at any level in the alimentary tract.

Dilatation by means of a radiopaque filiform and follower is a feasible alternative in such cases as the above, and is of definite value in all cases of esophageal dilatation in infants.

REFERENCES

1. Bokay, J. V.: Ueber die Behandlung der Langenveratzungen in Kindesalter nach Salzer, Wien. klin. Wchnschr. **37**: 282-285, 1924.
2. Jackson, Chevalier: Peroral Endoscopy and Laryngeal Surgery, The Laryngoscope Co., St. Louis, 1915; pp. 532-537.
3. Mixter, S. J.: Symposium on the Surgery of the Esophagus From the Standpoint of the General Surgeon, Tr. Am. Laryng. A. **31**: 342-348, 1909.
4. Plummer, H. S.: The Value of a Silk Thread as a Guide in Esophageal Technique, Surg., Gynec. & Obst. **10**: 519-523, 1910.
5. Tucker, G.: Cicatricial Stenosis of the Esophagus With Particular Reference to Treatment by Continuous String, Retrograde Bouginage With the Author's Bougie, Ann. Oto., Rhin. & Laryng. **33**: 1180-1223, 1924.
6. Vinson, P. P.: The Swallowed Silk Thread as a Guide in Esophageal Instrumentation, Arch. Otolaryng. **13**: 94-96, 1931.
7. Von Hacker: Zur Behandlung Tiefsitzender Narbenstricturen der Speiserohre durch Sondirung ohne Ende nach Temporarer Gastrostomie und Oesophagostomie, Wien. klin. Wchnschr. **7**: 455-457, 480-482, 1894.
8. Wangensteen, O. H.: Technical Suggestions in the Performance of Total Gastrectomy, SURGERY **25**: 766-775, 1949.

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†V. Mueller & Co.

THE TREATMENT OF A LINGUAL THYROID WITH RADIOACTIVE IODINE

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A LINGUAL thyroid is a rare clinicopathologic finding. Treatment has been surgical for all patients whose symptoms have warranted therapy. The various surgical procedures have been difficult because of the anatomic location, anesthetic problems, asphyxia, and hemorrhage. Myxedema has been a frequent postoperative complication. The following is a report of the successful treatment of a case of lingual thyroid with radioactive iodine. It is the first known case to be treated in this fashion and has afforded a rare opportunity to observe grossly the effects of radioactive iodine on the thyroid gland.

The historical aspects, embryology, anatomy, pathology, and surgical treatment of lingual thyroid have been very completely reviewed by Buckman,[4] Montgomery,[13] and Ray.[16] Since this last report, isolated case reports have appeared,[1-3, 5-8, 11, 12, 14, 17-23] with the addition of very little new knowledge.* In summary, the first case was described by Hickman[10] in 1869. The position of the lingual thyroid has been easily explained by its embryologic development beginning at the base of the tongue. Anatomically the aberrant gland is well encapsulated and supplied by the lingual arteries. Microscopically the aberrant gland has shared in all the normal and abnormal changes that occur in the thyroid situated in its usual position in the neck, including neoplasia.

When symptoms have warranted, the ectopic thyroid has been surgically approached anteriorly through the hyoid bone and mandible, laterally and intraorally. Most surgeons have more recently preferred the intraoral approach with intratracheal anesthesia. All agree on the hazards of anesthesia and the difficulty in the control of bleeding. Occasionally the external carotids have been ligated as a preliminary or concomitant operation. Often stage operations have been resorted to and tracheotomy has been frequently employed electively or by necessity. The end results have been good for the most part. Death has occurred rarely in the surgically treated patients reported upon in the literature. The principal postoperative complication following excision of the lingual thyroid is myxedema, as in most cases the patient's entire thyroid tissue was situated at the base of the tongue.

Presenting symptoms have been dysphagia, dyspnea, dysphonia, hemorrhage, and an annoying sense of a tumor in the throat. The symptoms often are minimal or absent, depending on the size of the gland. The appearance

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*Since submission of this paper for publication, Nachman, Crawford, and Bigger have described the use of I^{131} in the preoperative diagnosis of lingual thyroid. (Radioactive Iodine [I^{131}] in the Diagnosis of Lingual Thyroid, J. A. M. A. **140**: 1154-1156, 1949.)

grossly is a purplish-red, vascular, soft tumor with occasional areas of necrosis, inflammation, or granulation tissue. Approximately 275 cases have been reported to date, 75 per cent occurring in females. The case to be reported here is the first in 244,000 admissions to the Strong Memorial and Rochester Municipal Hospitals. In 11,900 autopsies and 4,200 cases of thyroid disease at these hospitals, there has been no other recorded case. Interestingly, the general incidence in the literature is one case for every 2,500 to 4,000 cases of thyroid disease.

The use of radioactive iodine during the past decade has added much to our knowledge of the physiology of the thyroid, and has been useful diagnostically and therapeutically in certain functional and neoplastic changes. There have been several excellent recent reviews[15] on this rather complex subject, a summary of which is beyond the scope of the present report. Specific mention should be made of the work of Hamilton and Lawrence[9] who produced almost complete destruction of the thyroid in dogs and rabbits with radioactive iodine. Clinically in the treatment of hyperthyroidism, overdosage with radioactive iodine will produce myxedema, indicative of thyroid destruction in the human being. Because of this recent knowledge, the surgical hazards mentioned previously, and its availability, radioactive iodine therapy was elected in the following case of lingual thyroid.

CASE REPORT

P. W., a 30-year-old white mother of three children, was first seen here* Feb. 12, 1946, with the complaint of a nasal quality in her voice, difficulty in swallowing, and a swelling in the back of the tongue of fifteen years' duration. The tumor had recently increased in size, seemed to become larger during upper respiratory diseases, and bled freely during pregnancies, requiring cauterization at another hospital. A biopsy was taken at another hospital in 1938 which revealed normal thyroid tissue beneath the mucosa at the base of the tongue with some tendency for colloid change (Figs. 1 and 2).

Physical examination revealed a well-developed and well-nourished woman without a palpable thyroid in the neck. At the base of the tongue there was a beefy nodular swelling about 4 cm. in diameter, purplish-red in appearance, and soft, without evidence of recent bleeding (Fig. 3). The basal metabolic rate was + 1 per cent. She was followed at frequent intervals and because of an increase in the severity of the symptoms, enumerated here, she was admitted to the Strong Memorial Hospital Sept. 5, 1946, for treatment with radioactive iodine (I^{131}, eight-day half life). Examination at this time revealed essentially the same findings at the base of the tongue. An oral test dose of 1.4 millicuries of I^{131} in 200 c.c. of water was given on Sept. 5, 1946, with marked concentration in the region of the base of the tongue (Fig. 4). This was followed by an oral therapeutic dose of 10 millicuries of I^{131} in 200 c.c. of water on Sept. 9, 1946. Again there was a marked concentration of the isotope at the base of the tongue (Fig. 5). The immediate excretion curves of I^{131} are shown in Fig. 6. The patient was discharged and followed at regular intervals. Repeated white blood counts failed to show any depression of the bone marrow. One month following treatment she gained ten pounds in weight, and a basal metabolic rate was -14 per cent two months later. At this time she showed definite signs of hypothyroidism and the mass at the base of the tongue seemed somewhat smaller and more discrete. She was given thyroid extract, .032 Gm. three times a day orally, with marked relief of the thyroprivic symptoms and the basal metabolic rate rose to + 12 per cent.

In May, 1947, she was admitted to the Strong Memorial Hospital for re-evaluation and study. Laboratory studies were all within normal limits. The thyroid nodule was smaller

*By Dr. John Morton.

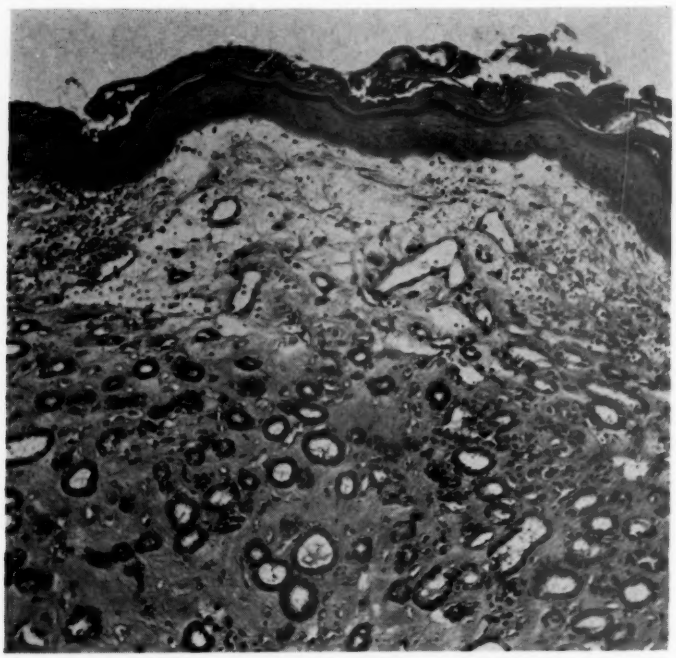

Fig. 1.—Microscopic appearance of lingual thyroid, 1938. (×100.)

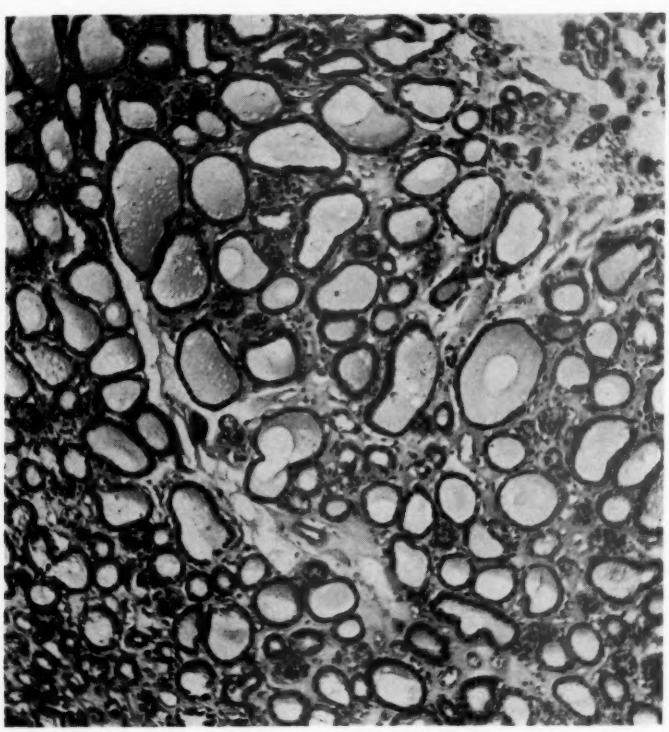

Fig. 2.—Microscopic appearance of lingual thyroid, 1938. (×100.)

than previously noted and it was felt that no further therapy was indicated. She was followed at three-month intervals with a slow and progressive decrease in the size of the lingual thyroid mass. Two years after treatment with I^{131}, on Sept. 16, 1948, under intratracheal gas-oxygen-ether anesthesia, the thyroid was biopsied. At this time under direct vision the mass was quite small measuring 2 cm. in diameter, and slightly elevated above the surface of the tongue. It was pale in appearance (Fig. 7). Microscopically the thyroid tissue showed atrophy and fibrosis (Figs. 8 and 9). She was last seen on May 19, 1949, at which time indirect laryngoscopy revealed a 1.5 cm. pale, avascular nodule at the base of the tongue (Fig. 10). Symptoms of dysphagia, dysphonia, hemorrhage, and the annoying feeling of a mass in the throat had disappeared. She still had, however, a nasal quality to the voice which, though decreased in intensity, was of the same quality as on first admission. She continued by necessity on thyroid extract, .032 Gm. three times a day, and was in otherwise excellent health.

Fig. 3.—Gross appearance of lingual thyroid with extreme vascularity, 1946.

DISCUSSION

One cannot help but be impressed by the difficulties encountered in the surgical treatment of a lingual thyroid. The use of radioactive iodine should prove to be a valuable form of therapy in lingual thyroid. Even if the reduction in the size of the thyroid tissue is not sufficient to alleviate adequately the symptoms, subsequent surgery should be made easier, because of the striking decrease in vascularity. In this instance the effective reduction in size of a lingual thyroid has been simply accomplished with no risk to the patient. This entity is so rare that few observers have the privilege of seeing or treating more than one such patient in a lifetime. It is hoped that this report will be useful to others who might have an opportunity to treat such a patient.

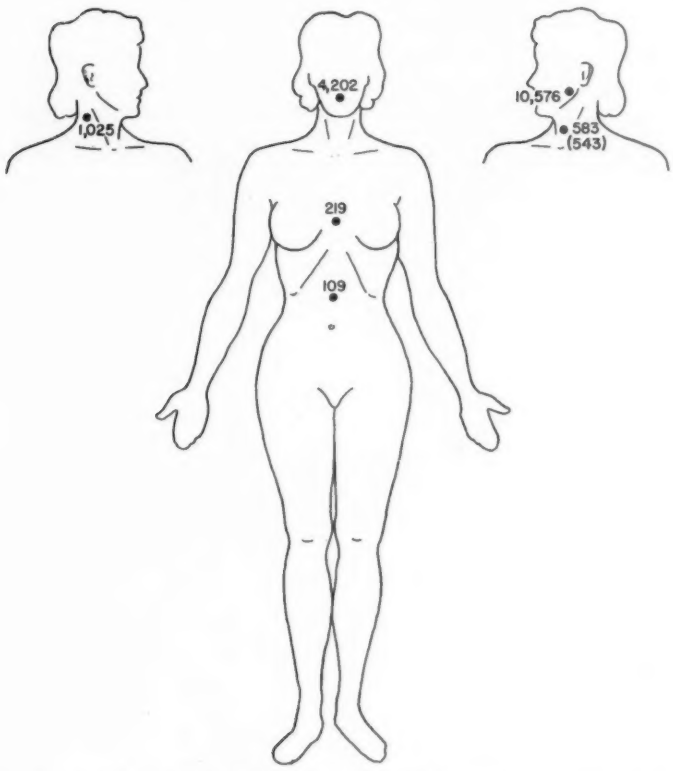

Fig. 4.—Geiger counts per minute following a 1.4 millicuries oral test dose of radioactive iodine. Note lack of concentration in usual position of thyroid in neck.

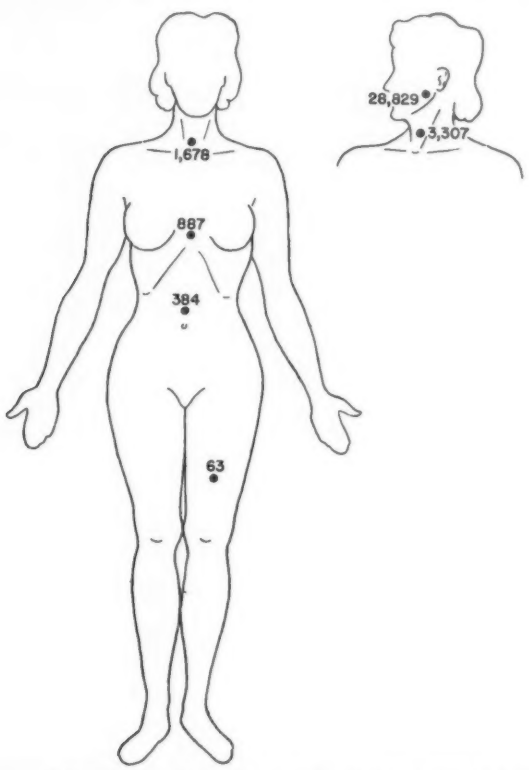

Fig. 5.—Geiger counts per minute following a 10 millicuries oral therapeutic dose of radioactive iodine. Note concentration in region of base of tongue.

This method of therapy adds to the growing list of experimental, diagnostic, and therapeutic uses of radioactive iodine. The progressive loss of vascularity, atrophy, and fibrosis of this lingual thyroid has been slow anatomically and extended over a period of two and one-half years before it was considered complete. Functional change was prompt, however, as evidenced by the early onset of symptoms of thyroprivus. From the amount of the radioactive material given, the amount excreted in the urine, the estimated size of the gland, the factors of radioactive decay, and the Geiger-Müller tube studies, it was possible

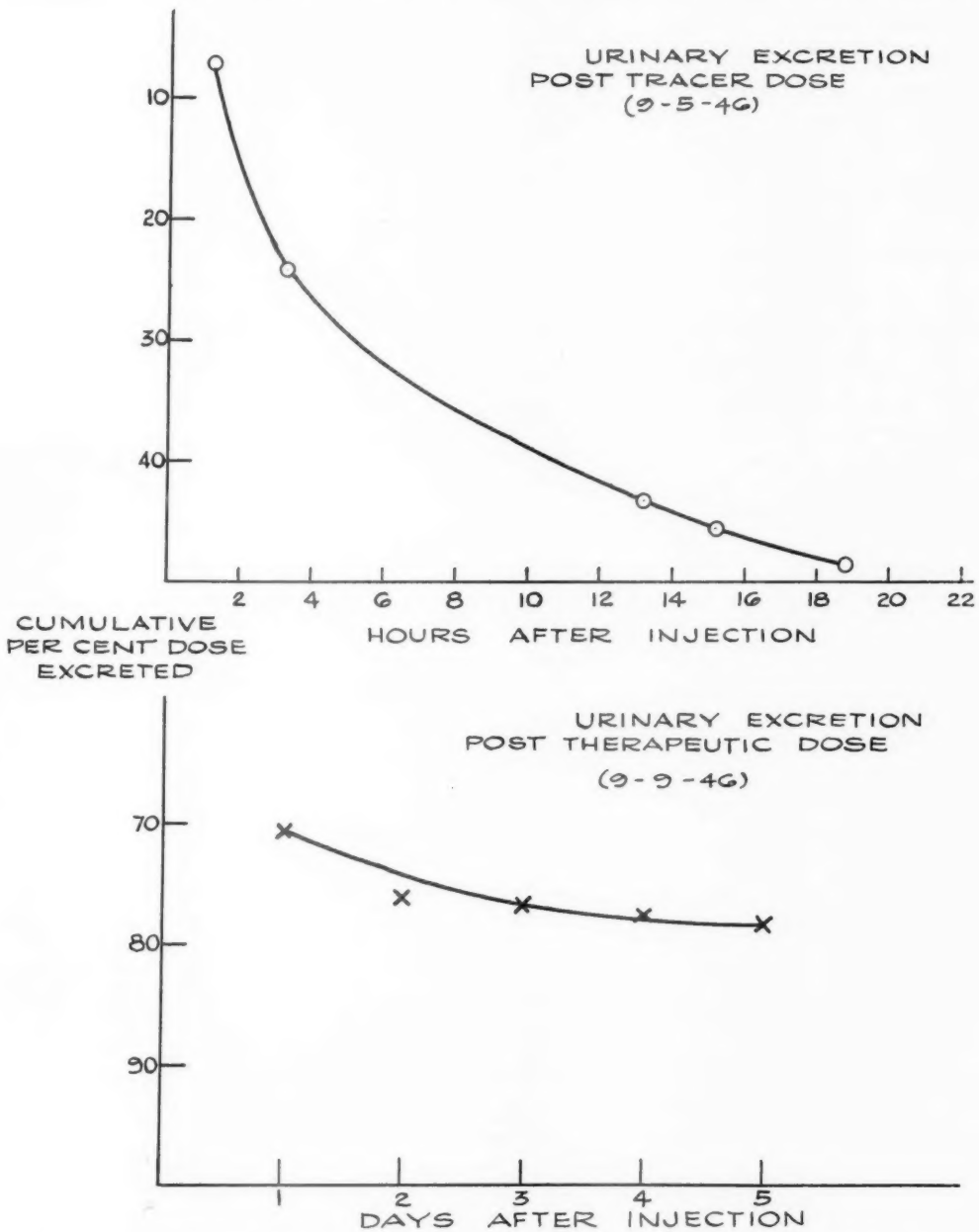

Fig. 6.—Urinary excretion curves of test and therapeutic doses of radioactive iodine.

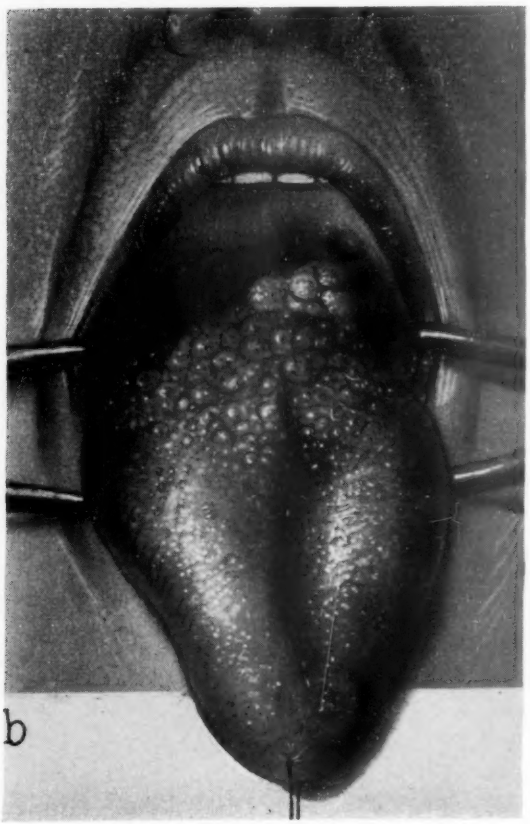

Fig. 7.—Gross appearance of lingual thyroid, 1948, two years after treatment with radioactive iodine. A marked decrease in vascularity.

Fig. 8.—Microscopic appearance of lingual thyroid two years after treatment with radioactive iodine. Marked atrophy and fibrosis. (×60.)

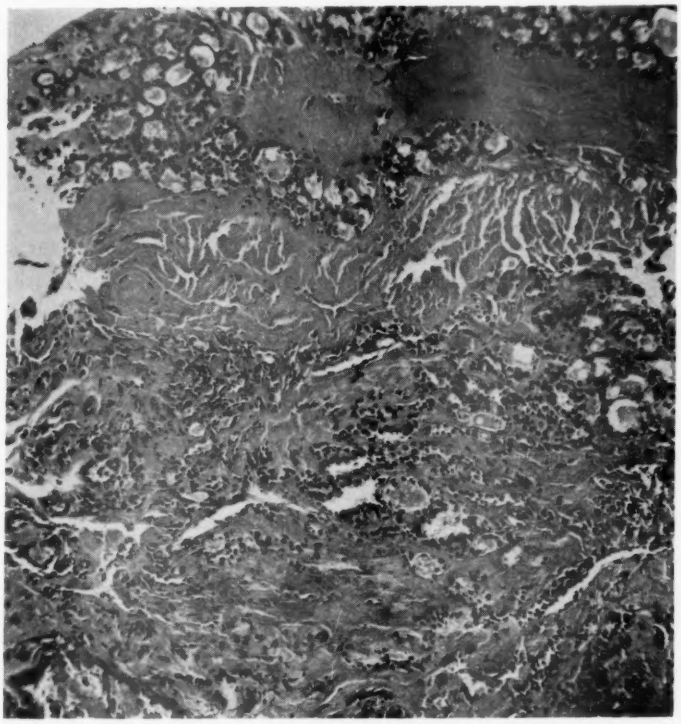

Fig. 9.—Microscopic appearance of lingual thyroid two years after treatment with radioactive iodine. (×100.)

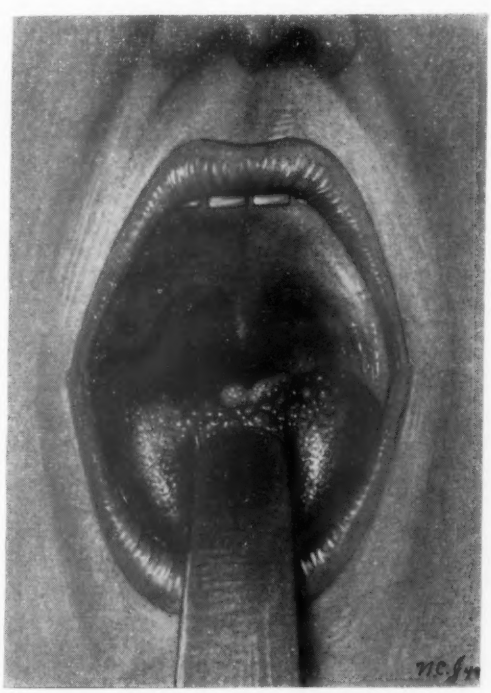

Fig. 10.—Gross appearance of lingual thyroid, May, 1949, thirty-two months after treatment with radioactive iodine with complete loss of gross vascularity.

to arrive at an estimate of the total radiation dose given to the lingual thyroid. This was estimated to be 11,000 roentgens equivalent physical. In the future, with greater knowledge of the effects of a given quantity of radioactive iodine on an accurately appraised mass of thyroid tissue, the complication of myxedema may be minimized.

SUMMARY AND CONCLUSIONS

A patient with lingual thyroid, successfully treated by radioactive iodine, is presented. Data concerning the use of the radioactive isotope and the gross and microscopic effects of this form of treatment on the lingual thyroid are recorded.

REFERENCES

1. Ardoin, P. S. G., and Frankfurt, P.: Goitre Lingual et Hypothyroidie, Presse méd. **45**: 921-922, 1937.
2. Bajkay, T.: Ueber die Zungengrundstrumen, Monatschr. f. Ohrenh. **76**: 260-268, 1942.
3. Bertoloni, G. M.: Sulla Ectopia della Tiroide alla base della Lingua, Riv. di clin. med. **5**: 343-351, 1946. (Supp. 2 margin, Otolaryng.)
4. Buckman, L. T.: Lingual Thyroid, Laryngoscope **46**: 765-784, 878-897, 936-955, 1936.
5. Cromartie, W. J., and Nelson, O. G.: Adenocarcinoma of Tongue Arising From Vestige of Median Anlage of Thyroid Gland. Report of a Case, Arch. Surg. **43**: 599-608, 1941.
6. Eidlin, D. J.: Ueber den Kropf der Zungenwurzl, Monatschr. f. Ohrenh. **71**: 332-336, 1937.
7. Foggie, W. E.: A Lingual Thyroid: Myxedema Following Its Removal, Edinburgh M. J. **48**: 662-668, 1941.
8. Gutgemann, A.: Beitrag zur Frage des Zungenkropfs, Zentralbl. f. Chir. **67**: 1282-1289, 1940.
9. Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-phosphorus and Radio-iodine, J. Clin. Investigation (Abstr.) **21**: 624, 1942.
10. Hickman, Wm.: Congenital Tumor of the Base of the Tongue Pressing Down the Epiglottis on the Larynx and Causing Death by Suffocation 16 Hours After Birth, Tr. Path. Soc. Lond. **20**: 160-163, 1869.
11. Landivar, A. F.: Bocio Lingual. Operatión—Curación (con Presentación de enferma), Bol. y trab., Acad. argent. de cir. **28**: 749-761, 1944.
12. Lemmon, W. T., and Paschal, G. W.: Lingual Thyroid, Am. J. Surg. **52**: 82-85, 1940.
13. Montgomery, M. L.: Lingual Thyroid, A Comprehensive Review, I to VIII, West. J. Surg. **43**: 661-669, 1935; **44**: 54-62, 122-128, 189-195, 237-247, 303-309, 373-379, 442-446, 1936.
14. Oberti, G.: Un Caso di Gozzo Linguale, Arch. ital. di chir. **58**: 373-380, 1940.
15. Rawson, R. W., Skanse, B. N., Marinelli, L. D., and Fluharty, R. G.: Radioactive Iodine. Its Use in Studying Certain Functions of Normal and Neoplastic Tissues, Cancer **2**: 279-292, 1949.
16. Ray, B. S.: Lingual Thyroid, Arch. Surg. **37**: 316-326, 1938.
17. Roman, D.: Lingual Thyroid (Lingual Goiter), J. Internat. Coll. Surgeons **4**: 213-216, 1941.
18. Rosedale, R. S.: Intralingual Thyroid: Discussion With Report of a Large Struma Presenting in the Anterior Part of the Tongue, Ann. Otol., Rhin. & Laryng. **45**: 1009-1018, 1936.
19. Rubin, H.: Aberrant Lingual Thyroid, Report of a Case, Am. J. Surg. **32**: 150-153, 1936.
20. Smith, C.: Lingual Thyroid, Arch. Otolaryng. **29**: 78-81, 1939.
21. Tessier, L. J.: Un Cas de Goitre Lingual, J. de L'Hôtel-Dieu de Montréal **5**: 301-304, 1936.
22. Villoria, L. L., Blanco, B. G., and Rivero, A.: Tiroides Lingual, Rev. san. y asist. social. **11**: 545-554, 1946.
23. Wapshaw, H.: Lingual Thyroid, A Report of a Case With Unusual Histology, Brit. J. Surg. **30**: 160-165, 1942.

THE USE OF HEPARIN IN THE PROPHYLAXIS OF PERITONEAL ADHESIONS

An Experimental Study

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THE problem of peritoneal adhesions is a concern to everyone who does abdominal surgery. In the past much thought and investigation have been directed to this subject and the problem has been approached from diverse, sometimes ingenious, angles. This is well summarized in the review of the literature by Boys[1] in 1942. This same author in conjunction with Lehman[2, 3, 4] published in 1940 the first of several reports on the experimental use of heparin introduced into the abdomen in an attempt to prevent the re-formation of divided adhesions. They worked principally with dogs, and, after a considerable amount of experimental data based on more than 170 experiments, concluded that heparin reduced adhesion re-formation to 35 per cent. In their control groups, which received nothing or comparable amounts of normal saline solution, amniotic fluid, or papain, more adhesions re-formed than were divided. They experimented with dosages and found it necessary for optimum results to administer heparin on each of three successive days, the first dose being given immediately postoperatively.

This promising experimental work was received with considerable interest at the time, and the authors were sufficiently encouraged to try out their method clinically. In 1941 they published a report of fourteen cases treated with heparin after the lysis of adhesions.[5] Seven of the cases were their own and seven were those of other surgeons who had become interested in the work. There was one fatality in this group which they attributed to poor judgment in the selection of the case, and in postoperative observation of the case. They emphasized that cases should be carefully selected and that heparin should not be used where there is oozing or granulation tissue present. They admitted that it would take years of observation of the late results of many cases before any conclusions could be drawn as to the clinical efficacy of the method. Following this clinical report there has been a surprising dearth of publications on either clinical or experimental use of heparin in the peritoneum. Massie[6] in 1945 reported a small series of seven clinical cases. One of them came to re-operation and no adhesions at the site were found. Fine and his co-workers[7] have used heparin in their irrigating fluid in cases of peritoneal lavage for renal shutdown to prevent adhesion formation around the drains. Recently Bloor and associates[8] reported a series of experiments on rabbits from which they concluded that heparin had little if any effect on the formation or re-formation of adhesions.

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The present study was begun in 1946, as an attempt to re-evaluate the experiments of Lehman and Boys in the uncontaminated peritoneal cavity of dogs. Some unpublished experiments carried out at the University of Pennsylvania,[9] which utilized a peritoneal window in cats and which apparently showed adhesion formation despite the presence of heparin, made this seem advisable.

METHODS

For these experiments small mongrel dogs, ranging in weight from 6 to 12 kilograms, were chosen. No discrimination was made in regard to sex or age, although the distribution was approximately equal in regard to sex, and the dogs in general were young adult animals. The anesthetic used was intravenous sodium nembutal. Strict aseptic technique was carried out throughout the experiments. The skin preparation consisted of shaving, soap and water cleansing, and painting with tincture of iodine. A wet technique of applying gloves, using Zephiran, was carried out and talcum powder was avoided in the sterilization of the gloves, to prevent any possible contamination of the peritoneal cavity with talc. The abdomen was entered through a right rectus muscle-splitting incision. Silk technique was used. Great care was taken to avoid disturbing the intestinal contents any more than necessary. Moist saline sponges and sponge forceps were used in handling the bowel. An area of the ileum approximately 20 cm. from the ileocecal junction was then scarified. With a curved cutting needle held in a needle holder, two series of closely spaced parallel scratches were made at right angles to each other, creating a gridiron scarification. Great care was taken to produce a uniform density of scratch marks, and the area covered was in each case a 6 cm. segment of bowel. The first experiments were done using scarification alone. It then became apparent that the combination of scarification plus the addition of a chemical irritant, namely tincture of iodine, was more efficient in producing adhesions, and for the bulk of the experiments this combined method was used. Scarification produced a raw, oozing bowel surface. Light pressure with a moist saline sponge sufficed to control any appreciable bleeding. Following this the iodine was applied to the area, care being taken to prevent soiling adjacent areas. The loop of ileum was then replaced in the abdomen and closure carried out. The peritoneum was closed with painstaking care, using a continuous mattress suture of No. 000 black silk, which everted the free edges of peritoneum and avoided inclusion of omentum and the ventral mesentery flap in the closure. This latter was not easy, as the ventral mesentery in the dog is a variable structure and has a great tendency to roll into the suture line as a stitch is pulled through. After the wound edges were carefully checked for bleeding points, the rectus sheath and skin were closed with interrupted sutures of the same material.

Three groups of experiments were set up. The first control group received nothing intraperitoneally. A second control group received 100 c.c. of normal saline solution intraperitoneally by paracentesis immediately after the opera-

tion, and on each of the two succeeding days. The third group received 100 c.c. of normal saline solution containing 30 mg. of heparin* immediately after operation and again on each of the two succeeding days.

In these experiments the plan for the administration of heparin was the same as that used originally by Lehman and Boys in their animal experiments. They found that it was necessary to administer heparin for at least three days to get the maximum effect. In their animal experiments they administered three daily single doses, while in their clinical cases they used two doses daily at twelve-hour intervals for a total of seven doses over three and one-half days. In the present work three daily single doses were used, although it would seem more effective, in view of the rather short-lived action of heparin, to use more frequent injections. The chief reason for this was that each administration of heparin to the dogs called for a general anesthesia and a separate paracentesis.

In setting up the experiments it was decided to restrict attention to a limited and constant area of peritoneum in order to be certain to produce uniform insult to the peritoneum and to eliminate variables, such as the disposition of surrounding organs, including omentum. Six weeks following operation the dogs were sacrificed and a careful study and recording of adhesions were made.

RESULTS

Table I is a compilation of the results. Thirty-seven dogs in all were operated upon. They were sacrificed and examined at the end of six weeks, with four exceptions. These latter were all in the group receiving heparin, and they were examined at 3½, 3½, 5, and 12 weeks, respectively. The three dogs examined earlier than six weeks represented deaths from intercurrent pulmonary infection. Six weeks was decided upon as an optimum interval, as by that

TABLE I

GROUP	NUMBER OF DOGS	NUMBER OF DOGS WITH ADHESIONS TO SCARIFIED ILEUM			
		MINIMAL	MODERATE	EXTENSIVE	TOTAL
I. Control	10	2	3	5	10 (100%)
II. Saline Control	11	0	5	3	8 (73%)
III. Heparin	16	1	0	0	1 (6%)

time adhesions should be well organized and definite entities. Microscopic study was made of the adhesions and revealed relatively young cellular connective tissue containing capillaries. It will be seen that all ten control dogs and eight of the eleven saline control group developed adhesions to the site of scarification, while in the group that received heparin only one dog out of sixteen showed any adhesions to the site. None of the four dogs examined at intervals other than six weeks developed adhesions.

In attempting to grade the extent of adhesion formation, investigators in the past have used various plans. Lehman and Boys suggested counting and meas-

*The heparin used was supplied by The Upjohn Company, Kalamazoo, Mich., in 10 c.c. vials containing 100 mg. of heparin.

uring the individual adhesions. Counting alone would not give a fair appraisal as it would not distinguish between a single filamentous band 1 mm. in diameter and a broad adhesive area 1 cm. in diameter, giving both equal weight. Accurate measurement of adhesions is a decidedly difficult task, as the shape of an adhesion varies considerably with the particular disposition of the involved structures at the time of measurement. The method adopted was for the examiner to make a subjective but critical estimate based primarily upon the area of bowel surface involved in the adhesions. On the basis of this, the particular experiment was given one of the following classifications: none, minimal, moderate, extensive. The one dog with adhesions in the heparin group showed minimal adhesions. Of the 10 dogs in control Group I, all of which showed adhesions, there were 2 classified as minimal, 3 as moderate, and 5 as extensive. Of the 8 dogs in the saline control Group II with adhesions, 5 were classified as moderate and 3 as extensive.

In general, adhesions were found principally to involve the great omentum and the scarified area of ileum. Other structures found adherent to the scarified ileum were; adjacent mesentery, adjacent loops of ileum, parietal peritoneum of the abdominal wall, abdominal wall incision, broad ligament of the uterus. On occasion the scarified loop had doubled on itself and become adherent, creating marked angulation of the bowel.

In addition to the adhesions to the scarified loop of ileum from the above structures, there were found in all three groups a not inconsiderable number of adhesions to the line of peritoneal closure in the abdominal wall incision. There were two structures about equally involved in these, the omentum and the vestigeal ventral mesentery. Approximately one-half the dogs in each of the three groups showed adhesions involving one or both of these structures and the incision.

Coagulation times were carried out using the capillary tube method and gave somewhat inconsistent results. In general, they showed only a slight rise in the coagulation time in the order of 3 to 4½ minutes, as compared to a normal of 1½ to 2 minutes.

In this series there were no serious complications or deaths attributable to heparin. Two minor wound hematomas were present which readily resolved. One dog showed temporary prostration and paresis of the hindquarters, which cleared completely forty-eight hours following withdrawal of heparin. His coagulation time twenty-four hours after the last dose of heparin was thirty minutes, which was surprisingly high.

DISCUSSION

The results show a clear-cut difference in adhesion formation between the heparin group and the two control groups. Only one of 16, or 6 per cent, of the heparinized dogs had adhesions, and these were minimal. Of the 10 control dogs in group I, 100 per cent had adhesions, while of the 11 dogs in control Group II receiving saline solution, 8, or 73 per cent, exhibited adhesions. In the two control groups the adhesions tended to be somewhat more extensive

in the group receiving nothing intraperitoneally. In view of the relatively small groups involved, however, this difference is not considered significant. In the dogs in which adhesions formed there was noted a marked individual factor in the extent of adhesion formation, which others have found also, and which is in accord with clinical experience.

Microscopic study confirmed the gross observation that the adhesions were in all cases organized connective tissue and not merely fibrin. The interval of six weeks was purposely chosen to allow the adhesions to become firmly established. The natural evolution of adhesions is not too well known. The supposed sequence of events is a laying down of fibrin, followed by a growth into it of connective tissue elements to form a definite tissue between the two involved surfaces. It would appear that fibrin is a necessary precursor to every fibrous adhesion. On the other hand, every fibrinous adhesion need not go on to organization and the formation of a fibrous adhesion. Indeed, it is highly likely that many do not, as it has been frequently observed that an abdomen with many fresh fibrinous adhesions at a later date shows marked or even complete resolution of them. The eventual fate of a true fibrous adhesion is not too well known. Although many must be permanent, it is quite conceivable that some, especially the narrow bands and cords, become progressively more attenuated with the movements of the intestines until they finally disappear. These experiments shed no light on the life history of adhesions.

In the method used to produce adhesions it was apparent from observation of the healed areas in the dogs that did not develop adhesions, that the original trauma left many islands of viable mesothelium between the scarifications, and that healing took place by the growth of mesothelial cells from these islands to bridge the abraded areas. This situation is roughly analogous to that following division of adhesive bands and sheets where there is similarly a relatively narrow area to be reperitonealized. It is not, however, comparable to the situation following the separation of two broadly adherent surfaces where a broad area completely denuded of peritoneum results. In the latter instance it is hardly to be expected that a three-day period of heparinization would be sufficient to permit reperitonealization without adhesion formation.

It is to be noted that adhesions to the abdominal wall incision were encountered with equal frequency in all three groups. These were not included in the results in Table I, because other extraneous factors exist here which are not present at the experimental site, such as: accidental incorporation of ventral mesentery and omentum in the suture line, a gap in the suture line, and the presence of unabsorbable suture material. In only one instance was the scarified bowel adherent to the abdominal incision and this was included in the results of Table I. Even if all adhesions at the incision were included in the results, there would still be a marked difference in adhesion formation in the three groups, in the same direction, although there would be less animals in the heparin group with no adhesions whatsoever.

SUMMARY AND CONCLUSIONS

Scarification and chemical irritation of a measured segment of ileum in dogs produced adhesions in 100 per cent of control animals, and in 73 per cent of animals receiving saline solution intraperitoneally. In dogs which were subjected to the same insult but in which heparin was instilled intraperitoneally daily for three days, adhesions to the scarified bowel resulted in a single instance, or 6 per cent. On the basis of these experiments it is felt that heparin instilled intraperitoneally is effective in preventing adhesions to the scarified ileum of dogs.

REFERENCES

1. Boys, F.: Prophylaxis of Peritoneal Adhesions, Review of Literature, SURGERY **11**: 118-168, 1942.
2. Lehman, E. P., and Boys, F.: Heparin in the Prevention of Peritoneal Adhesions, Ann. Surg. **112**: 969-974, 1940.
3. Lehman, E. P., and Boys, F.: Experimental Prevention of Intraperitoneal Adhesions With Heparin; Third Report, SURGERY **12**: 236-241, 1942.
4. Boys, F., and Lehman, E. P.: Experimental Studies on Peritoneal Adhesions; Fourth Report, Sulfanamides With and Without Heparin, Ann. Surg. **118**: 612-618, 1943.
5. Lehman, E. P., and Boys, F.: Clinical Use of Heparin in the Peritoneum in the Prevention of Adhesions, Arch. Surg. **43**: 933-945, 1941.
6. Massie, F. M.: Heparin in Abdomen; Clinical Report, Ann. Surg. **121**: 508-517, 1945.
7. Fine, J., Frank, H. A., and Seligman, A. M.: The Treatment of Acute Renal Failure by Peritoneal Irrigation, Ann. Surg. **124**: 857-878, 1946.
8. Bloor, B. M., and others: The Effect of Heparin Upon Intra-abdominal Adhesions in Rabbits, Ann. Surg. **126**: 324-331, 1947.
9. Ravdin, I. S.: Personal communication.

TUBERCULOSIS OF THE STOMACH

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TUBERCULOSIS of the stomach is a rare clinical entity. Walters, Kirklin, and Clagett[1] stated that, "It is one of the rarest manifestations of tuberculosis in the body." Broders[2] reviewed the literature as far as 1917 and found enough histologic or bacteriologic evidence to be accepted as adequate for the diagnosis in 167 cases. Good[3] compiled the cases reported up to 1931 and found 194 cases acceptable. Chaffin[4] furthered this study and to the end of 1937 found 54 cases definitely proved (demonstration of the tubercle bacillus) and 157 probable cases (typical histologic picture but no acid-fast bacillus present), which brought the total to 211 cases. Since this compilation, Clagett and Walters,[5] Ackerman,[6] Zelman,[7] Hartz and Van der Sar,[8] Sullivan and associates,[9] Windwer,[10] and probably others have added new cases to the total.

In 11,480 consecutive autopsies at Cook County Hospital, 2 cases of tuberculosis of the stomach were found; only 1 case was encountered in 75,000 surgical specimens.[9] Popoff[11] cited Crawford and Sawyer, who did not once find gastric tuberculosis in 1,400 autopsies of tuberculous subjects. Only 1 case appeared in the records of 21,000 admissions to the Jewish Hospital in Brooklyn from 1913 to 1944.[11] Three cases of tuberculosis of the stomach were discovered in a series of 7,416 consecutive gastric operations at the Mayo Clinic.[3] The reported ages affected by this disease have varied from less than 1 year to over 70 years old, but it is uncommon beyond 40 years of age. The ratio of males to females with this disease is about 2 to 1; of adults to children (15 years of age and younger) is approximately 5 to 1.[12]

For reasons unknown the stomach is highly immune to tuberculous infections. It is similar in this respect to the pancreas, the thyroid gland, the heart, the ovaries, and the salivary glands. It is logical to assume that tuberculous infections of the stomach would be high if we recall the routine clinical use of gastric washings to obtain evidence of acid-fast bacilli in suspected cases of tuberculosis and as Chaffin suggested, "Recall the fundamental character of the act of swallowing saliva, the necessity good manners imposes incessantly upon all of us, tuberculous or not." Many hypotheses have been advanced in an attempt to explain the rarity of gastric tuberculosis. It has been postulated that the stomach is protected by the activity of the gastric juice, but this has been refuted by the finding that in almost every case of advanced tuberculosis the gastric acidity is diminished. Against this also is the fact that gastric juice has no effect on the tubercle bacillus unless it is in contact for at least twelve hours. Virchow believed the answer lay in the scarcity of lymphatic supply of the stomach wall and according to Klebs in the sparcity and depth of lymph follicles in this area (quoted from Binder and associates).

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To support this latter contention is a fact that there are more abundant lymph follicles in the pyloric region where tuberculosis is more commonly found. Clagett and Walters stated that no one factor is entirely responsible for the immunity of the stomach to tuberculous infection. It is probable that a break in the mucosa is one of the causes. Hartz and van der Sar, however, have often observed superficial erosions without specific histologic features in stomachs of patients dying from pulmonary tuberculosis.

The sources of infection usually listed in the literature are: (1) Primary, by direct infection of the mucosa; (2) hematogenous; (3) extension from extragastric lesions through the serosa; (4) lymphogenous. It is doubtful if a primary type of infection exists. Good[3] stated, "From an academic standpoint, primary tuberculosis of the stomach has yet to be seen" and "observations by investigators lead to the conclusions, on the basis of information available at present, that the inclusion of the primary type is not justified" (Binder and co-workers).

The main types of tuberculosis of the stomach which may be distinguished pathologically are: (a) Miliary, in which the stomach contains single caseous tubercles located in the serosa or submucosa and is a part of the generalization of the disease. (b) Ulcerative, which is the most frequent. In this type there is usually one, rarely more, ulcers which may vary from 1 to 20 cm. in diameter. The edges are undermined, ragged, thickened, and edematous. The floor is covered with necrotic debris, usually gray or yellow. The regional nodes are often caseous or necrotic. Ulcers are more common in the pylorus and more frequently on the lesser curvature. The tuberculous granulations around the margins and the healing of the ulcer lead to thickening and scarring of the pylorus resulting in constriction of the pyloric ring and obstruction. The ulcerating type is found in about 80 per cent of the cases of stomach tuberculosis. (c) Hypertrophic. This is a rarer type of gastric tuberculosis. Tuberculosis hyperplasia is more commonly found in the region of the lower ileum or large bowel and may manifest itself by a palpable mass. (d) Extragastric forms of tuberculosis which invade the stomach.

There are no characteristic clinical symptoms to aid in the diagnosis. The condition usually mimics a peptic ulcer, gastric syphilis, or a gastric carcinoma, and a misdiagnosis is made more certain by laboratory and x-ray findings resembling one of these lesions. Negative serology will usually exclude the diagnosis of syphilis of the stomach. The earliest symptoms may be those of a gastritis with loss of appetite and a feeling of fullness or pain in the epigastrium. Vomiting is one of the most common symptoms but in the tuberculous patient this can be misleading as it may be caused by some extragastric involvement such as tuberculous peritonitis or meningitis. A daily elevation of temperature is suggestive. One should suspect the diagnosis in all tuberculous patients with gastric symptoms and findings in spite of its apparent rarity. Had we considered our patient's past tuberculosis history and interpreted the numerous calcified nodes found in roentgenograms (Fig. 1), a tentative diagnosis of gastric tuberculosis could have been made. The diagnosis in almost every instance has been made at necropsy or operation.

CASE REPORT

A. C., a Mexican man, aged 32 years, entered St. Mary's Hospital on April 26, 1947. The chief complaints were vomiting, epigastric pain, and weight loss. He had had tuberculous adenitis involving mainly the cervical nodes since childhood. In 1945 he was confined to a tuberculosis sanatorium in California for a period of eight months. He had been a heavy drinker for the past twelve years, consuming from three to four pints of wine or "whatever I could get" daily. He admitted "stomach trouble" for the past five to six years; during the past year the patient had increased abdominal pain, often following a

Fig. 1.—Calcified glands shown observed during x-ray examination of the gastrointestinal tract.

drinking bout. The onset of this illness dated back about three months previous to this hospital admission when dyspepsia and epigastric distress became more marked and constant. During this period of time he had lost thirty pounds in weight. For the past month he vomited after each meal and often after the ingestion of fluids. He had noted tarry stools and coffee-ground vomitus during the past two weeks.

Physical examination showed a poorly nourished man appearing acutely ill, anemic, and much older than his stated age. Both sides of the neck were scarred with keloid healing, and hard fixed lymph nodes of the anterior and posterior chains could be palpated. No draining sinuses were present. There was a soft systolic cardiac murmur present, most audible at the apex, which was transmitted over the entire left side of the chest. Lung sounds were normal. There was epigastric tenderness. Voluntary abdominal rigidity made accurate palpation difficult. No masses were found. Bowel sounds were normal. Tempera-

ture was 101.2° F. and blood pressure was 110/65. Laboratory studies showed the following: hemoglobin, 5 Gm.; red blood cells, 2,290,000; and white blood cells, 10,400. Anisocytosis and marked hyperchromia were observed. Kahn and Wassermann tests gave negative results. Urine was normal. Icteric index was five units. Serum protein was 6.55 mg. per 100 c.c. (Patient was dehydrated at the time this was taken.) Total nonprotein nitrogen was 40 mg. per 100 c.c. Stool examination was positive for occult blood.

The following x-ray studies were made. Chest: There were a number of perihilar calcifications and a number of calcified nodes observed in the right side of the neck. Gastrointestinal series: The duodenal cap was deformed and the duodenum stringlike. There was more than a twenty-four hour retention of food material in the stomach. There were a number of calcified cystic lesions in the epigastric region, the largest of which was approximately 3.5 by 4.5 cm. From the examination, it appeared that the patient had a pyloric ulcer with severe duodenitis. (Figs. 1 and 2.)

Fig. 2.—X-ray plates illustrating the stringlike duodenum with deformity of the duodenal cap. The tuberculous lesion of the stomach is not apparent in these films and the diagnosis of duodenitis with duodenal ulcer was made preoperatively.

The patient received daily blood transfusions with infusions containing vitamins and amino acids. Wangensteen nasal suction was started and continued until April 30, 1947, at which time he was able to assimilate fluids by mouth; red blood cell count was 3,180,000 with a hemoglobin of 8.5 Gm.

The preoperative diagnosis was peptic ulcer with associated duodenitis and tuberculous adenitis.

On May 3, 1947, under N_2O_2 and ether anesthesia the abdomen was opened through a transverse incision.

The periaortic, perigastric, and many of the mesenteric lymph glands were hard and enlarged. One was removed for biopsy and it was found to be composed of calcified caseous material. The stomach was three times its normal size. The gall bladder was pale, edematous, and plastered to the anterior side of the pyloric portion of the stomach. The gall bladder was freed and it was found that this covered a large perforated ulcer about the size of a quarter of the anterior portion of the stomach just proximal to the pyloric ring. A biopsy was taken of the ulcer and frozen section showed the lesion to be of an inflammatory nature. The interior of the duodenum could be visualized and it was observed to be scarred, stenosed, and its tissues were brittle. Due to the inflammatory reaction present in the duodenum, it was deemed inadvisable to resect this portion of the stomach as a safe closure of the duodenum seemed impossible. The perforation in the stomach was closed by suturing the gall bladder and omentum back over the perforation, and a subtotal gastric resection was accomplished by resecting about two inches above the pyloric

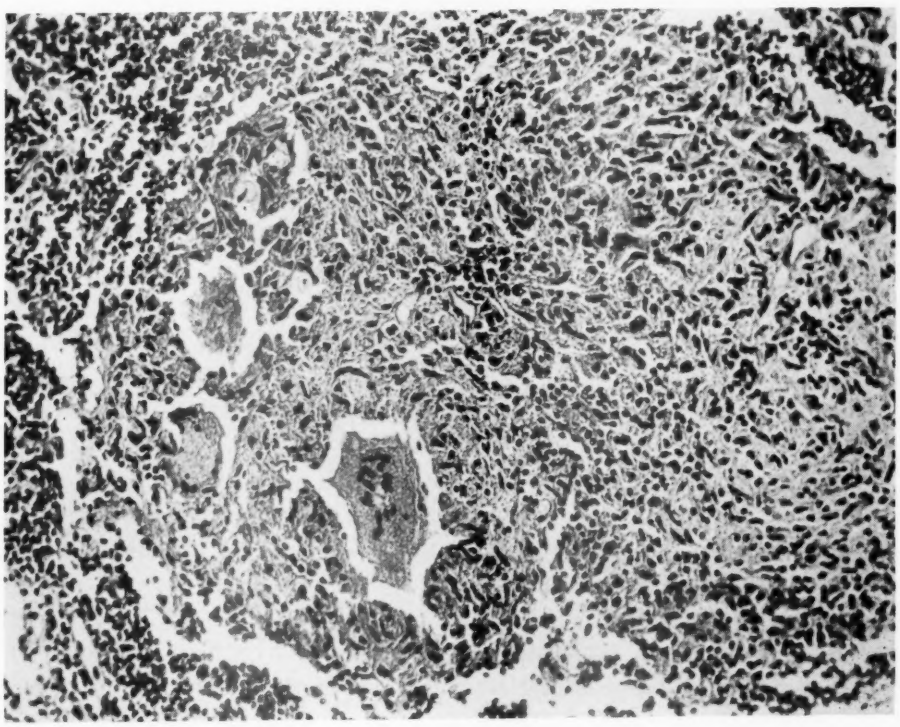

Fig. 3.—Photomicrograph of the biopsied section from the stomach exhibiting the characteristic pattern of tuberculosis.

ring, removing about three-fourths of the stomach. The proximal end of the stomach was closed and an isoperistolic, antecolic Hoffmeister anastomosis was made between the stomach and the first portion of the jejunum. A jejunostomy was done for postoperative nutrition and the abdomen was closed without damage. The wound healed by first intention. Ambulation was allowed starting on the first postoperative day. The patient was discharged on May 15, 1947, on the twelfth postoperative day.

Pathologic examination of the excised portion of the stomach and the tissue removed from the ulcer was made. Gross examination of the stomach revealed no evidence of ulcer. Microscopic examination of the stomach sections showed no evidence of ulceration. There was an increase in round-cell infiltration of the mucosa. Biopsied tissue from two sections

of the ulcer showed a granulomatous reaction. Numerous giant and epithelial cells were present. No foreign bodies were seen. There were a few small focal areas of necrosis in relationship to the giant cells and there was considerable lymphoid hyperplasias. Acid-fast stains showed no acid-fast bacilli. (Fig. 3.)

Diagnosis was granulomatous gastritis, probably tuberculosis.

The patient was last seen on July 24, 1947, at which time he had gained twenty-two pounds, had a nurmal blood count, was eating all foods without discomfort, and a stool was negative for occult blood. On July 30, 1947, a conversation with his sister informed us that the patient had again taken up serious drinking and had returned to California. During the past year the patient worked on a fishing boat running to Alaska. He was last heard from in December, 1948. In a letter to his family he stated that he was feeling well and was in Miami, Fla.

DISCUSSION

As noted here, it is most doubtful if primary tuberculosis of the stomach occurs. It may exist, however, in conjunction with other primary lesions of the stomach, making its nest in a bed prepared for it by carcinoma or gastric ulcer. Rentschler and Travis[13] reported a case where sarcoma and tuberculosis of the stomach existed simultaneously. In a review of 368 reported cases of tuberculosis of the stomach, Clagett and Walters found thirty cases of associated gastric carcinoma. In the case reported by Hartz and associates they wrote: "The possibility of a secondarily infected peptic ulcer has to be considered." Clagett and Walters believed that a pre-existing pyloric ulcer is a definite factor and stated that tuberculosis of the stomach "occurs through erosion, eccymosis, gastritis, ulcer and carcinoma." It seems quite probable that the patient reported herein, with his alcoholic habits and past history, had a pre-existing ulcer.

"There is no need clinically to differentiate tuberculosis of the stomach from chronic organic lesions in order to institute the proper treatment."[3] Those cases having definite symptoms and findings need surgical therapy. Resection of the involved portion of the stomach is the operation of choice. In our case this was not done for it was thought too hazardous. The extent of the resection depends upon the tuberculous involvement. Watson and associates,[14] for instance, successfully performed a total gastric resection with an esophagojejunostomy for a case of hourglass stomach due to hyperplastic gastric tuberculosis. The clinical diagnosis had been gastric carcinoma.

Gastroenterostomy has been advocated when the risk is too great for the performance of a gastric resection. The exclusion operation, as done in our case, would seem to have an advantage over a gastroenterostomy in that the infected scarred portion of the stomach is protected, placed at rest, and more likely to heal.

Perforation of a tuberculous ulcer is apparently rare as perforation has been reported in only three instances.[5] If the assumption is true that many tuberculous infections are superimposed on pre-existing gastric ulcers, more perforations should be expected. In our patient a perforation had occurred which apparently was a chronic, slowly progressive affair.

There is a very meager follow-up study of the reported cases. In most of the reports the follow-up observation has not extended at most over a period

of a few years. It would be of interest to know the incidence of recurrence after ten or twenty years. A number of these patients die from the original tuberculosis infection. A follow-up study on the reported patient will be of interest as we can find no reference where a Devine exclusion operation has been done for tuberculosis of the stomach. The immediate results have been excellent and should they continue to be satisfactory, we would advocate this operation as being the safest and most simple procedure for those lesions involving the antral portion of the stomach and duodenum where complete resection is inadvisable.

REFERENCES

1. Walters, W., Kirklin, B. R., and Clagett, O. T.: Proc. Staff Meet., Mayo Clin. **11**: 83, 1936.
2. Broders, A. C.: Surg., Gynec. & Obst. **25**: 490, 1917.
3. Good, R. W.: Arch. Surg. **22**: 415, 1931.
4. Chaffin, L.: SURGERY **5**: 187, 1939.
5. Clagett, O. T., and Walters, W.: Arch. Surg. **37**: 505, 1938.
6. Ackerman, A. J.: Am. J. Roentgenol. **44**: 59, 1940.
7. Zelman, J.: Am. Rev. Tuberc. **41**: 809, 1940.
8. Hartz, P. H., and van der Sar, A.: Am. Rev. Tuberc. **47**: 46, 1943.
9. Sullivan, R. C., Francona, N. T., and Kirshbaum, J. D.: Ann. Surg. **112**: 225, 1940.
10. Windwer, C.: Rev. Gastroenterol. **13**: 38, 1946.
11. Popoff, N. W.: Arch. Path. **31**: 220, 1941.
12. Binder, I., Ruby, V., and Shuman, B. J.: Gastroenterology **5**: 474, 1945.
13. Rentschler, C. B., and Travis, R. C.: J. A. M. A. **102**: 686, 1934.
14. Watson, G. W., Flint, E. R., and Stewart, M. J.: Brit. J. Surg. **24**: 333, 1936.

LYMPH FISTULAS IN TRAINED DOGS

An Experimental Technique

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DURING the past two and one-half years we have been engaged in a series of experimental studies of flow and composition of lymph coming from a special organ or body region of the dog.[1, 2, 3] In nearly all of these studies it was necessary that the rate of lymph flow be measured continuously, and that specific constituents be determined in lymph samples obtained at frequent collection intervals. The majority of experiments were on trained dogs that had recovered from the anesthesia used for the surgical procedure of cannulation of the lymphatic. The purpose of this report is to describe the instruments and technique that we have used in these studies.

PLASTIC TUBING CANNULAE

Late in 1945, at the suggestion of one of us (F. C. M.), we began some studies on hepatic lymph. It was soon apparent that, in order for us to obtain sufficient hepatic lymph for analysis, we should have to find a better material out of which to make cannulae than glass. We found that the rigidity of capillary-sized, paraffin-coated, glass cannulae caused them to angulate and obstruct the hepatic lymphatic, or that clotting of lymph soon blocked the cannulae. We searched for a tubing in which lymph would not readily clot. It seemed desirable, also, that the tubing be easily sterilized and transparent, and that it produce minimal tissue reaction. If such tubing could be found, it was hoped that, by placing one end in the lymphatic at operation and bringing the other end to the body surface through a stab wound, lymph would continue to flow from the tube for long periods after recovery from operation.

A suitable tubing was found almost at once, a plastic tubing used industrially for insulation of electric wires of small diameter and known commonly as polyvinyl tubing. Polyvinyl is a synthetic resin which is a copolymer of vinyl chloride and vinyl acetate combined with a plasticizer and is extruded in a wide variety of wire sizes commercially. The plasticizer is laked out by many organic solvents including those present in traces in living tissues. As a result, within one day, tubing used for lymph cannulae becomes opaque and relatively stiff. The gradual stiffening of the tubing does not seem to interfere with its effectiveness as a cannula however, probably because the tube stiffens in situ. In all other respects we have found polyvinyl tubing eminently suitable for lymphatic cannulae. Its flexibility minimizes the hazard that it will cause a kink in the lymphatic. Its transparency permits the surgeon to watch the flow of lymph and to detect blood and air bubbles.

The smooth uninterrupted bore of the tube permits a rapid washing out of thromboplastic substances which are undoubtedly liberated during the

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cannulation of the duct. If a good flow of lymph is maintained for the first few hours, there is subsequently little trouble with coagulation of the lymph in the tube. The flow of lymph from the intestinal lymphatic or the thoracic duct may be materially increased by oral administration of water or saline solutions. An occasional clot may be successfully removed from the tube, but if the obstruction remains long it may cause the opening of collateral lymph channels with subsequent diminution or absence of flow from the cannulated lymphatic. Polyvinyl tubing cannot be autoclaved but may be sterilized by boiling water. However, our practice is to sterilize it by immersion for twenty minutes in 1:1,000 aqueous Zephiran solution because the tubing is slightly soft after it is boiled in water. We have not observed any tissue reaction, that is, adhesions, peritoneal or pleural thickening, exudate or increased vascularity about polyvinyl tubes, even those which have been left in place for as long as two and one-half years. The only tissue reaction that we have observed is a very thin fibrous capsule surrounding the tube where it traverses muscle or connective tissue layers.

Polythene tubing is satisfactory for cannulation of some lymphatics. In most respects it is like polyvinyl tubing but has the advantage that it does not become more rigid in tissue and the disadvantage that, except in capillary sizes, it is too stiff.

The size of tubing used in most of our work on dogs for lymphatic cannulation has been wire size No. 24. In the thoracic duct, however, we often use tubing as large as wire size No. 20.

TECHNIQUE OF CANNULATION

The most efficient method of learning where to find the lymphatic that one wishes to cannulate is to inject T-1824 (Evans blue) dye into the organ or body part drained by that lymphatic. Once the surgeon has learned the location of the lymphatic it is easy for him to recognize it without such aid. He will shortly learn, however, that it is easier to find lymphatics in thin subjects than in fat, and less difficult in young not fully developed animals than in the mature or aged. He will learn, also, that the state of body hydration affects the conspicuousness of lymphatics but it will take him longer to learn that the lymphatics of a larger animal or large species are not proportionately larger than those in smaller animals.

Having learned where to find the lymphatic one should approach it directly and quickly, giving himself as much exposure through the operative incision as he needs. The exposure of the lymphatic itself, however, should be restricted to an exposure, by blunt dissection, of the presenting or nearest surface. If a lymphatic is dissected out to such an extent that it is lying free, without support from surrounding tissues, one is chagrined to find that it collapses to the diameter of a thread when it is incised for the introduction of the cannula. We have learned that, if we dissect enough merely to expose the nearest surface of the lymphatic, the lymphatic does not collapse to a thread when it is incised, but to a flattened tube in which the hole of incision is quite visible.

It is relatively easy to expose the presenting surface of a lymphatic trunk. Before an attempt is made to cannulate the trunk, however, it is necessary to plan the point of incision in the lymphatic and to place a loose ligature about the lymphatic at some point proximal to the incision. The hazard of placing the ligature is that a branch entering the lymphatic from behind will be torn. If this happens the lymphatic will collapse, and it will be hard to cut a small hole in the lymphatic without cutting completely through it. The purpose of the ligature when it is eventually tied is not only to hold the cannula in the lymphatic but to occlude small parallel lymphatics which are usually not visible but may be present about the main trunk. Because of the latter purpose the ligature is not placed close to the lymphatic but around tissue surrounding the lymphatic.

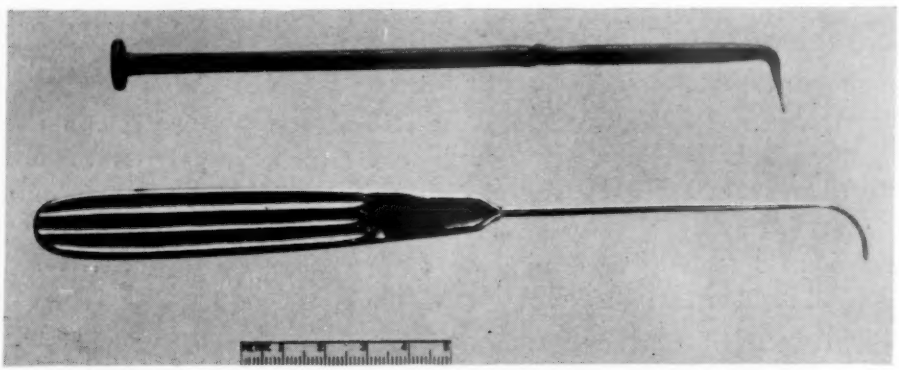

Fig. 1.—The upper instrument is the seeker, which is inserted into the lymphatic, after it has been opened, as a guide for the introduction of the plastic tubing cannula. It is made of dark blue glass (plungers of tuberculin syringes fused together). The end has been bent at a sharp angle, drawn to a small diameter, and the tip fire-polished.

The lower instrument is the tool used for exposure of a lymphatic by blunt dissection. The shaft is tempered, round, and tapered slightly. The tip, which is flat and blunt, has a needle-eye perforation.

The instrument used for stripping tissue from the presenting surface of the lymphatic and for passing the ligature is one that has been long used in our laboratory for delicate blunt dissections (Fig. 1). It resembles a ligature carrier. The handle is hollow and light in weight and the shaft, which is tempered, is tapered almost to the tip. The tip is flattened and hollow ground, and its edge is about the thickness of a paring knife blade. A needle eye hole is present near the end of the tip. Just behind the tip the shaft is curved to one-quarter circle, the curve being in the shape of a parabola with the flat portion on the shaft side. The advantage of this instrument in blunt dissection is that the flat, thin, rounded tip slides between tissue planes while it pushes aside small blood and lymphatic vessels.

The only other special instruments required for cannulation are a glass seeker and a pair of very fine, sharp-pointed scissors which cut perfectly at the tip. The scissors are used for cutting a hole in the lymphatic; the seeker is used to hold the hole in the lymphatic open while the cannula is inserted. The seeker consists of a glass rod bent to approximately a right angle and drawn to the diameter of a bristle at one end (Fig. 1). Several such instru-

ments, bent at slightly different angles, should be on hand for each cannulation. The tip of the seeker should be smoothly polished by fire. Because lymphatics and lymph are transparent we have made seekers from dark blue glass rods (plungers from broken tuberculin syringes) instead of colorless transparent glass.

The final steps in cannulation are the incision of the lymphatic and the introduction of the plastic tubing cannula. These steps are not to be undertaken, however, until all preparations have been made. It does not behoove the operator to take his eyes off the lymphatic for long once it has been opened. The plastic tubing should be filled with saline solution containing a few units of heparin and the tip of the tubing should be cut at an angle of about 45 degrees. Scissors, seeker, the tubing, and smooth thumb forceps should be placed at the edge of the incision. The surgeon's assistant should have the field well exposed and should not shift his hands in the slightest degree. Good anesthesia and illumination are necessary.

The exposed presenting wall is cut at the proper point just distal to the not yet tied ligature with the sharp-pointed scissors. Immediately, the lymphatic collapses and the field is flooded with lymph. A dry gauze sponge placed near the lymphatic will usually suffice to absorb most of the lymph. Then, the tip of the seeker is inserted into the lymphatic in a retrograde direction and, if possible, through the valve above. Great care is required for piercing of the valve because of the great danger of piercing the back wall of the lymphatic. The seeker is withdrawn slightly and lifted, in order to cause the opening in the lymphatic to gape. The tubing is held in the other hand with the smooth forceps and the beveled tip is inserted into the opening behind the seeker. As the seeker is withdrawn, the tubing is pushed into the lymphatic. Usually, to get the tip beyond the valve one must rotate the tubing slightly. If the cannulation is successful, lymph will at once begin to drop from the distal end of the tubing.

The final steps in the operation are simple. The previously placed ligature is tied. Usually this ligature serves to hold the tubing securely in place but sometimes it is necessary to place another anchoring ligature. Before the incision is closed the distal end of the plastic tubing is led out through a tiny stab wound and tied to a suture placed in the skin. It will require the surgeon's ingenuity to place, and sometimes to anchor in position, the length of tubing between the lymphatic and the stab wound, and to place the stab wound in the proper location. One must be certain that traction or angulation of the tubing and lymphatic will not occur when the dog changes position or adjacent organs shift with respiratory or visceral movements.

Methods of collection of lymph and of protection of the tubing from damage are best worked out by experience. Our usual method is to place the dog immediately after operation in a cage, in which it can stand, sit, or lie but cannot turn about, and to keep it there while the study is in progress. The free end of the tubing is placed in a glass receptacle containing a few units of heparin and the receptacle is placed in a thermos bottle containing ice.

Efforts to start lymph flowing again after it has stopped are usually futile. If the lymph is pink, indicating the presence of blood, it usually will not flow long. A clot in the tubing can usually be removed by gentle suction but care is required or air will get in the tubing. Sometimes a change in the dog's position, or exercising the dog, will start lymph flow. Eventually, however, in the best preparation, flow will stop because the lymphatic is blocked and collateral flow of lymph has developed. Several factors favor a good lymph flow: short operation time, avoidance of unnecessary dissection and trauma especially in the region of the lymphatic and the region or organ it drains, and placement and anchoring of the cannula so that tension or angulation of the lymphatic will not occur. The carrying out of some other experimental procedure, such as cholecystectomy, ligation, or cannulation of the common bile duct or pancreatic ducts, or cannulation of both the thoracic duct and hepatic or intestinal lymphatic, imposes great hazards and reduces the chances of success.

ANATOMIC EXPOSURE OF VARIOUS LYMPATHICS

One may easily familiarize oneself with the anatomic position of a lymphatic by surgical exposure of the area in which it is to be found and injection of T-1824 dye into the parenchyma of the organ or part which the lymphatic drains. Within a few minutes the afferent lymphatics, lymph nodes, and efferent trunks draining lymph nodes will in turn become dark blue. It will be seen that lymphatics entering the node are numerous and of thread-like smallness. Obviously they are too small to be cannulated by the technique described and, moreover, if they could be cannulated, little would be gained. The flow of lymph would be small and, because an imposed resistance to flow (a cannula) in that lymphatic would cause lymph to be diverted into an adjacent lymphatic, very brief. On the other hand the trunks draining lymph nodes are much larger and frequently single.

We have found that the following exposures are best for the lymphatics that we have used in our studies.

Thoracic Duct.—We have abandoned cannulation of the duct where it empties into the left subclavian vein, the usual point at which it is cannulated. We found that too often the right or accessory thoracic duct was sizable and that there was a rich anastomosis between the main duct and the right duct and between these ducts and a system of cervical lymphatics which empty into the great veins of the superior mediastinum at many points. We found that the thoracic duct in the lower part of the thorax was frequently a single trunk and that when the duct was cannulated a short distance above the diaphragm a greater and longer-continued flow of lymph was obtained. We expose the duct by opening the left side of the thorax through an incision in the eighth interspace and retracting the lower lobe of the lung upward after dividing its diaphragmatic ligament. The duct, which lies between the aorta and the vertebral bodies, is exposed by ligating and dividing one to three intercostal arteries. Almost no dissection is required to find the duct in the small amount of fatty tissue behind the aorta. The ligature, which holds the can-

nula in place, is passed around the entire mass of fatty tissue behind the aorta. When it is tied, it will occlude the main duct at the point of cannulation as well as visible and invisible accessory ducts. Frequently we are able, if the tip of the cannula has a very obtuse bevel, to slip the tubing down the duct for a considerable distance and even into the cisterna chyli, because the thoracic duct has few or no valves. A short loop of tubing is left in the thorax and the remainder is brought out through an intercostal stab wound. Flow of lymph from the thoracic duct of a medium-sized dog at rest is usually at the rate of 3 to 5 c.c. per ten minutes. Thoracic duct lymph during rest is composed almost entirely of hepatic and intestinal lymph because there is almost no lymph flow under these conditions from the hind legs.

Hepatic and Intestinal Lymphatics.—The hepatic and intestinal lymphatics are reached through a midline abdominal incision extending from the xiphoid to well below the umbilicus. The right side of the base of the duodenal mesentery is exposed by having the assistant grasp the first portion of the duodenum in the right hand between thumb and fingers and retract it in a caudal and ventral direction. The intestines are then placed behind the duodenal mesentery and the duodenum and mesentery are covered by a large moist pack. The assistant places the flat of his hand on the moist pack and keeps the viscera retracted and the duodenal mesentery taut, thus exposing the entire base of the mesentery.

The hepatic lymphatics are at the cephalic end of the duodenal mesentery, near the foramen of Winslow. The afferent lymphatics, which are threadlike structures and very numerous, emerge from the hilus of the liver and travel caudally along the portal vein until they enter the hepatic lymph node. This lymph node is near the border of the foramen of Winslow, just dorsal to the portal vein. Frequently, there is a second hepatic lymph node and occasionally a third, both usually ventral to the portal vein, which frequently drain the pancreas and the duodenum as well as the liver. Usually there is one sizable efferent lymphatic trunk leaving the hepatic lymph node and passing dorsally, parallel and caudal to the hepatic artery, to the base of the mesentery. This is the lymphatic trunk which we cannulate. The ligature which holds the cannula in place includes tissue surrounding this trunk and, when it is tied, occludes other small lymphatic trunks coming from the node. We are in the habit of placing similar ligatures in the tissue caudal to the lymph node in order to occlude lymphatics which may be entering the hepatic node from pancreas and duodenum, or traveling toward another hepatic lymph node.

The intestinal lymphatic trunk is found in close relationship to the superior mesenteric artery and usually consists of several trunks which anastomose with each other freely and which twine about the artery and sympathetic nerves while traveling toward the base of the mesentery. Placement of the ligature about these trunks, so that all will be occluded, is made very difficult because of the necessity of avoiding the mesenteric artery and its branches and the splanchnic nerves.

The rate of flow of both hepatic and intestinal lymph is usually 1.5 to 3 c.c. per ten minutes. Hepatic lymph is clear, even during digestion, and has a

slight but definite golden color. Intestinal lymph from a fasting dog is slightly cloudy, and from a dog which has been fed it is opaque white. If hepatic lymph becomes milky, it is being contaminated by intestinal (duodenal) lymph. Mixing of hepatic and intestinal lymph can usually be seen at the time of operation in the common vessel (an arm of the cisterna chyli) lying close to the vena cava into which both lymphatics empty.

Hind Leg Lymph.—The abdomen is opened by a low abdominal incision. Because the penis makes such an incision undesirable in male dogs, we have usually used female dogs in these studies. Furthermore, because of the position of the vena cava and iliac veins, we have always cannulated the left iliac lymphatic. This trunk is usually found just beneath the peritoneum lying to the left of, and parallel to, the lower portion of the aorta, cephalad to a string of lymph nodes in the iliac region. Usually there is one main trunk and several small trunks, all of which are occluded by the ligature which holds the cannula in place. Lymph obtained from the iliac lymphatic is clear and colorless. Rate of flow, when the dog is lying or standing quietly, is very low. When the dog moves its left hind leg or exercises, flow increases abruptly and often to a very high rate.

The length of time after operation during which lymph flows freely and uninterruptedly varies considerably in our experience. In the case of a thoracic duct fistula, five to eight days is the usual time, while twelve hours to two days is all that a hepatic lymph fistula will flow. Intestinal and hind leg lymphatic fistulas usually flow for one to three days.

The cannulation of lymphatic trunks from other abdominal viscera may at times be practical. On one occasion we discovered and cannulated a large pancreatic lymphatic trunk. Other anomalies of the lymphatic system may be present and give the surgeon opportunities which it would be almost impossible to realize in the average dog.

SUMMARY

A lymph fistula, which will continue to flow after recovery of the animal from anesthesia, may be made by cannulating a lymphatic trunk with sterile, small diameter, flexible, plastic tubing, either polyvinyl or polyethylene tubing. Clotting of lymph does not occur readily in such tubing. Frequently lymph will flow for several days and permit study of flow and composition of lymph under many experimental conditions. A technique of surgical exposure and cannulation of the thoracic duct in the chest and of the hepatic, intestinal, and iliac lymphatic trunks in the abdomen has been described in detail.

REFERENCES

1. Cain, J. C., Grindlay, J. H., Bollman, J. L., Flock, Eunice V., and Mann, F. C.: Lymph From Liver and Thoracic Duct: An Experimental Study, Surg., Gynec. & Obst. **85**: 558-562, 1947.
2. Grindlay, J. H., Cain, J. C., Bollman, J. L., and Flock, Eunice V.: Experimental Studies of Liver and Thoracic Duct Lymph, Minnesota Med. **31**: 654-655, 1948.
3. Flock, Eunice V., Cain, J. C., Grindlay, J. H., and Bollman, J. L.: Phospholipids of Lymph Following Feeding of Fat to Dogs (Abstr.), Federation Proc. **6** (pt. 2): 252, 1947.

Editorial

Support the Man, Not the Method

THE American layman, accustomed to the engineering miracles of our industrial age, often becomes impatient with the inability of medical science to solve the riddle of malignancy and the degenerative diseases. All physicians have watched the powerful man of business, impotent while a member of his family is dying of cancer, unable to understand why "industrial know-how" has not cracked the cancer problem. He believes that money, instruments, and technical skill should be able to solve any medical problem.

Scientific medicine has made tremendous progress. Since 1900 the life expectancy at birth has been raised from 40 to almost 70 years. Yet this progress is due chiefly to better control of the infectious diseases. The life expectancy of the man of 60 is now only *three days* longer than it was in 1900.

Large sums, unparalleled in the history of scientific medicine, have been allocated in recent years for research in cancer and the degenerative diseases. These sums have become available chiefly because these problems have caught the public's fancy; and the public, not comprehending the need for support of basic research, has given to the problem at hand. The money has become available but can it be used wisely?

In large part we are attacking these problems much as the industrialist would attack them. We are setting up huge institutions, with elaborate technical facilities and unlimited material resources. But have we trained and are we training the inquiring scientific minds to use them? And are we giving those minds the freedom they require? The problems will be solved by the minds of men—not by the means or the method.

The medical research worker has always been grossly underpaid in worldly goods. His fellow physician engaged in the practice of medicine under a competitive economic system of supply and demand has invariably made more money. The result has been that two types of physicians have made a career of medical research: (1) those who entered for the love of investigation, and (2) those who entered because they were incompetent or unsuited to the practice of clinical medicine. It is true that many bright young medical students, potential solvers of medical problems, are lured away from a career in research by the financial attractions of clinical practice. It is also true that many have not been drawn into research because they have not had sufficient contact with stimulating research workers. Some incompetent medical men have found "a way out" in research and have become "hangers-on" around universities. The medical

student, in turn, is often led to emulate his clinical teachers, not because they make more money, but because they seem more competent persons. Students are told that they should not go into clinical medicine unless they get along well with people. This is true. But it does not mean that students who do not get along well with people will make better research workers.

The answer seems obvious. Make a career in medical research an attractive one financially, but apply rigid standards of intelligence, integrity, and industry to the selection of the research worker. In this way will be built up a group of medical research workers who will attract the best minds of the medical profession. Pay them well and free them from the burden of insecurity. They will solve the problems of cancer and the degenerative diseases. They will demand and get the facilities with which to work. Support the man, not the method.

—I. S. Ravdin.